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- (71) Applicant (for all designated States except US): **DI-ADEXUS, INC.** [US/US]; 343 Oyster Point Boulevard, South San Francisco, CA 94080 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SUN, Yongming** [CN/US]; 551 Shoal Drive, Redwood City, CA 94065 (US). **LIU, Chenghua** [CN/US]; 1125 Ranchero Way #14, San Jose, CA 95117 (US).
- (74) Agents: **LICATA, Jane, Massey et al.**; Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ 08053 (US).
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(54) Title: COMPOSITIONS AND METHODS RELATING TO HEPATIC SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acid molecules and polypeptides present in normal and neoplastic hepatic cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions containing the nucleic acid molecules, polypeptides, antibodies, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating hepatic cancer and non-cancerous disease states in hepatic, identifying hepatic tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered hepatic tissue for treatment and research.

## COMPOSITIONS AND METHODS RELATING TO HEPATIC SPECIFIC GENES AND PROTEINS

This application claims the benefit of priority from U.S. Provisional Application  
5 No. 60/343,137, filed December 21, 2001, which is herein incorporated by reference in its entirety.

### FIELD OF THE INVENTION

The present invention relates to newly identified nucleic acids and polypeptides  
present in normal and neoplastic liver and/or hepatic cells, including fragments, variants  
10 and derivatives of the nucleic acids and polypeptides. The present invention also relates to  
antibodies to the polypeptides of the invention, as well as agonists and antagonists of the  
polypeptides of the invention. The invention also relates to compositions comprising the  
nucleic acids, polypeptides, antibodies, post translational modifications (PTMs), variants,  
derivatives, agonists and antagonists of the invention and methods for the use of these  
15 compositions. These uses include identifying, diagnosing, monitoring, staging, imaging  
and treating hepatic cancer and non-cancerous disease states in hepatic, identifying hepatic  
tissue and monitoring and identifying and/or designing agonists and antagonists of  
polypeptides of the invention. The uses also include gene therapy, therapeutic molecules  
including but limited to antibodies or antisense molecules, production of transgenic  
20 animals and cells, and production of engineered hepatic tissue for treatment and research.

### BACKGROUND OF THE INVENTION

While relatively rare in the United States and Canada, hepatocellular carcinoma  
(HCC) is the eighth-most common cancer and the leading cause of cancer death in the  
world. Yu, M.C. *et al.*, *Can. J. Gastroenterol.* 14(8): 703-09 (2000); Bookstein, R. *et al.*,  
25 *Semin. Oncol.* 23(1): 66-77 (1996). Malignant primary hepatic tumors constitute two to  
three percent of primary cancers in the United States, with HCC accounting for 90% of  
malignant primary tumors of the liver in adults. Anderson, B.B. *et al.*, *J. Nat'l Med. Ass'n*  
84(2): 129-35 (1992). Outside of North America, regions of the world particularly at risk  
are the East, Southeast Asia, and sub-Saharan Africa. Yu *et al.*, *supra*. In China, for  
30 example, HCC is the second-most cause of cancer mortality, accounting for 130,000  
deaths annually. Tang, Z.Y. *et al.*, *Ann. Chir.* 52(6): 558-63 (1998). HCC is now  
becoming a serious problem in the United States, principally due to patients with cirrhosis



secondary to the hepatitis C virus developing liver cancer. Jeffers, L., *J. Nat'l Med. Ass'n* 92(8): 369-71 (2000).

Although our understanding of the etiology of HCC is undergoing continual refinement, research in this area points to a number of risk factors. In developed countries with populations at low risk for liver cancer, the hepatitis B virus (HBV) and hepatitis C virus (HCV) may be responsible for up to 75% of all liver cancer; in developing countries where HBV is prevalent, it may account for 60% of cases, with HCV playing a role in less than 10% of cases. F. Xavier Bosch, *Global Epidemiology of Hepatocellular Carcinoma, in Liver Cancer* 23 (Kunio Okuda & Edward Tabor, eds. 1997); see also Pei-Jer Chen & Ding-Shinn Chen, *Hepatitis B Virus and Hepatocellular Carcinoma, in Liver Cancer* 29 (Kunio Okuda & Edward Tabor, eds. 1997). Cirrhosis, which is considered by some to be a preneoplastic condition, is associated with three fourths of HCC cases. Swan N. Thung and Michael A. Gerber, *Cirrhosis and Hepatocellular Carcinoma, in Liver Cancer* 155 (Kunio Okuda & Edward Tabor, eds. 1997). Alcohol consumption and cigarette smoking are both risk factors for liver cancer, with a combined 1.2 to 2-fold risk, although cigarette smoking is thought to play a relatively minor role. Bosch, *supra* at 23-24. In developed countries, oral contraceptives have been linked to a two-fold to five-fold risk of liver cancer; in countries where HBV is relatively rare, the long-term usage of oral contraceptives may be responsible for as many as half of all liver cancer cases in women. *Id.* at 24. In Africa and certain areas of China and Southeast Asia, the incidence of liver cancer is correlated with predictions of the consumption of aflatoxin, a carcinogenic DNA intercalator generated by molds growing on spoiled food. *Id.* at 25; Gerald N. Wogan, *Aflatoxin Exposure as a Risk Factor in the Etiology of Hepatocellular Carcinoma, in Liver Cancer* 51 (Kunio Okuda & Edward Tabor, eds. 1997).

Despite recent progress in understanding the molecular and genetic causes of HCC, our understanding of these factors is nonetheless limited. Michael Geissler *et al.*, *Molecular Mechanisms of Hepatocarcinogenesis, in Liver Cancer* 59 (Kunio Okuda & Edward Tabor, eds. 1997). Researchers have theorized that abnormal expression of proto-oncogenes, or the expression of mutant variations of these genes (oncogenes), may lead to the transformation of neoplasms. *Id.* Moreover, induction of apoptosis and alteration of the "p53 tumor suppressor gene-dependent cell cycle checkpoint function" are thought to be involved in HCC as well. *Id.* It has also been postulated that DNA hypomethylation may work as an epigenetic mechanism that participates in the transformation of

hepatocytes. *Id.* Research is currently being performed to determine the possible role HBV and HCV in interfering with the proper function of tumor suppressor genes and in causing mutations in those genes. Edward Tabor, *The Role of Tumor Suppressor Genes in the Development of Hepatocellular Carcinoma*, in Liver Cancer 89 (Kunio Okuda &

- 5 Edward Tabor, eds. 1997). Research is also exploring how liver inflammation and cirrhosis caused by HCV may act as “promoters” in the progression of HCC. *Id.*

The links between certain genetic and acquired diseases of liver metabolism and liver cancer, however, are well-established, particularly those diseases in which chronic liver injury and cirrhosis are hallmark features. Geissler *et al.*, *supra* at 60-61; Yves

10 Deugnier & Bruno Turlin, *Other Causes of Hepatocellular Carcinoma*, in Liver Cancer 97 (Kunio Okuda & Edward Tabor, eds. 1997). These diseases include (1) hematochromatosis, (2)  $\alpha$ 1-antitrypsin deficiency, which results from a variant gene on chromosome 14q3, (3) type I tyrosinemia, (4) porphyria cutanea tarda, and (5) alcoholic cirrhosis. Geissler, *supra* at 60; Deugnier & Turlin, *supra* at 102.

- 15 Like many cancers, HCC is more readily treatable when detected early. Michael C. Kew, *Clinical and Nonimaging Diagnosis of Hepatocellular Carcinoma*, in Liver Cancer 315 (Kunio Okuda & Edward Tabor, eds. 1997). Unfortunately, screening for liver cancer is made difficult because symptoms and physical signs of the disease do not occur until its very late stages. *Id.* The absence of clinical manifestations of early-stage
- 20 liver cancer may be attributable to several factors: (1) the position of the liver deep in the peritoneal cavity, such that tumors cannot be readily felt, (2) the liver’s vast functional reserves, which do not allow symptoms to appear until much of the organ has been replaced by carcinoma, and (3) HCC metastasizes in the late stages of the disease. *Id.*

- Routine screening for HCC typically involves the use of ultrasound, in
- 25 combination with the determination of serum levels of  $\alpha$ -fetoprotein (AFP). Walter J. Burdette, *Cancer: Etiology, Diagnosis, and Treatment* 108 (1998); Yang, B. *et al.*, *J. Cancer Res. Clin. Oncol.* 123(6): 357-60 (1997). Due to its ability to provide (1) excellent contrast resolution, (2) multiplanar images, and (3) characterization of cancerous lesions based on signal intensities in a variety of pulse sequences, magnetic resonance
- 30 imaging (MRI) is becoming the modality of choice for screening patients for HCC. Sharma, R. & Saini, S., *J. Comput. Assist. Tomogr.* 23 Suppl. 1: S39-44 (1999); Masaaki Ebara, *MRI Diagnosis of Hepatocellular Carcinoma*, in Liver Cancer 361 (Kunio Okuda & Edward Tabor, eds. 1997). Computed tomography (CT) has also proven effective at

detecting HCC, particularly in cases where ultrasound is ineffective due to scar tissue, intervening bones, or air in the gut. Nyung Ihn Choi, *CT Diagnosis of Liver Cancer*, in Liver Cancer 371 (Kunio Okuda & Edward Tabor, eds. 1997). In fact, contrast-enhanced CT's ability to diagnose HCC does not differ significantly from MRI, although MRI is slightly superior in locating cancerous lesions that are 2 cm or smaller. *Id.* at 363. Hepatic angiography, while supplanted to some extent by ultrasound, CT, and MRI, remains useful in preoperative evaluation and in providing vascular maps. Kenichi Takayasu, *Hepatic Angiography*, in Liver Cancer 347 (Kunio Okuda & Edward Tabor, eds. 1997).

10 While a highly sensitive and specific marker would significantly facilitate HCC screening, no such marker has been discovered. Kew, *supra* at 325. Elevated serum level of AFP is a useful diagnostic indicator of HCC, but it is susceptible to false positives and false negatives. *Id.* at 325-26. Des- $\gamma$ -carboxy prothrombin has been touted as a "better" HCC marker than AFP, but one study reports that AFP is both more sensitive and more  
15 specific than des- $\gamma$ -carboxy prothrombin. *Id.* at 327. Tumor-associated isozymes of  $\gamma$ -glutamyl transferase, which are not detectable in normal serum, are highly specific but lack sensitivity. *Id.* While a number of other markers have been studied, none are sufficiently specific and sensitive to use in routine screening of HCC. *Id.* at 327-28.

Once HCC has been diagnosed, treatment decisions are made in reference to the  
20 stage of cancer progression. A number of the techniques employed to stage HCC are identical to those used to screen for HCC, including ultrasound, MRI, and CT. Hann, L.E. *et al.*, *Semin. Surg. Oncol.* 19(2): 94-115 (2000). With the use of tissue-specific contrast reagents, MRI has begun to undermine the role of CT portography in preoperative staging, and may soon completely supplant it. Sharma & Saini, *supra*. Researchers have also  
25 found that laparoscopy, in combination with laparoscopic ultrasonography, is also effective in preoperative staging. Gouma, D.J. *et al.*, *Scand. J. Gastroenterol. Suppl.* 218: 43-9 (1996). As in the case of screening, highly sensitive and specific markers would be of great assistance in staging HCC, yet none are presently available. Researchers have explored the use of soluble intercellular adhesion molecule-1, soluble interleukin-2  
30 receptor, interleukin 6, and anti-p53, but none of these potential markers was found useful. Parasole, R. *et al.*, *Clin. Cancer Res.* 7(11): 3504-09 (2001).

Several classification systems for staging hepatic cancer are currently used, including the TNM and the Okuda systems. Farinati, F. *et al.*, *Cancer* 89(11): 2266-73

(2000). The TNM system, devised by the Union Internationale Contre le Cancer, is divided into several stages, each of which evaluates the extent of cancer growth with respect to primary tumor (T), regional lymph nodes (N), and distant metastasis (M). Fleming *et al.* eds., *supra* at 3. The TNM system will be discussed in further detail here.

5        Stage 1 is characterized by a single tumor of 2 cm or less in greatest dimension, without vascular invasion (T1), with no regional lymph node metastasis (N0) and no distant metastasis (M0). *Id.* at 94-95. Stages II and IIIA differ from stage I only with respect to tumor category. *Id.* Stage II involves tumor category T2, which may be either (1) a single tumor of 2 cm or less in greatest dimension, with vascular invasion, (2)  
10        multiple tumors in only one lobe, all 2 cm or less in greatest dimension, with no vascular invasion, or (3) a single tumor of more than 2 cm in greatest dimension, without vascular invasion. *Id.* Stage IIIA involves tumor category T3, which may be either (1) a single tumor of 2 cm or more in greatest dimension, with vascular invasion, (2) multiple tumors in only one lobe, all 2 cm or less in greatest dimension, with vascular invasion, or (3)  
15        multiple tumors in only one lobe, any of which are more than 2 cm in greatest dimension, with or without vascular invasion. *Id.*

      Stage IIIB involves any one of the T1, T2, or T3 categories, metastasis to regional lymph nodes (N1), but no distant metastasis (M0). Stage IVA is characterized by tumor category T4, which may be either (1) multiple tumors in more than one lobe of the liver,  
20        (2) involvement of a major branch of the portal or hepatic veins, (3) invasion of nearby organs other than the gallbladder, or (4) perforation of the visceral peritoneum, and any N category with no distant metastasis (M0). *Id.* Lastly, stage IVB involves any T category, any N category, and distant metastasis (M1). *Id.*

      Once the HCC has been staged, typical treatment includes resection, percutaneous  
25        ethanol injection, and transcatheter arterial embolization. Shuichi Okada, *Chemotherapy for Hepatocellular Carcinoma*, in Liver Cancer 441 (Kunio Okuda & Edward Tabor, eds. 1997). Indeed, surgical resection of the carcinoma(s) is the first line of treatment for HCC, assuming that no extra-hepatic metastasis has been identified, Kunio Okuda *et al.*, *Treatment Selection*, in Liver Cancer 436 (Kunio Okuda & Edward Tabor, eds. 1997), and  
30        transplantation should always be considered in managing HCC, Burdette, *supra* at 111. Treatment with radiation, chemotherapeutics, hormones, and interferon have not proven consistently effective in curing HCC. Llovet, J.M. *et al.*, *Liver Transpl.* 6(6 Suppl. 2): S11-5 (2000). As for radiation, the amount of radiation necessary to achieve an adequate

response may be more than healthy hepatic cells can tolerate, Burdette, *supra* at 113, and as for chemotherapy, no individual anticancer agent or regimen of agents displays a response rate exceeding 20%, Okada, *supra* at 441.

New approaches involving immunotherapy are also being investigated, and these approaches fall within two general categories: specific immunotherapy and nonspecific immunotherapy. Daniel Shouval, *Immunotherapy for Hepatocellular Carcinoma, in Liver Cancer* 471 (Kunio Okuda & Edward Tabor, eds. 1997). As for specific strategies, researchers have targeted HCCs via monoclonal or polyclonal antibodies which recognize antigens on the cancer cell surface; these antibodies are either “free” or are joined to chemotherapeutic or biological molecules. *Id.* As for nonspecific strategies, researchers have explored using interferon- $\alpha$  and  $\gamma$ , lymphokine-activated killer cells, tumor necrosis factor, and antibodies bound to radioactive isotopes. *Id.* While promising, these strategies are still experimental, with much research yet to be done before they can become part of a standard treatment regimen for HCC. *Id.* at 477.

From the foregoing, it is clear that procedures used for detecting, diagnosing, monitoring, staging, prognosticating, and preventing the recurrence of HCC are of critical importance to the outcome of the patient. Moreover, current procedures, while helpful in each of these analyses, are limited by their specificity, sensitivity, invasiveness, and/or their cost. As such, highly specific and sensitive procedures that would operate by way of detecting novel markers in cells, tissues, or bodily fluids, with minimal invasiveness and at a reasonable cost, would be highly desirable.

Accordingly, there is a great need for more sensitive and accurate methods for predicting whether a person is likely to develop HCC, for diagnosing HCC, for monitoring the progression of the disease, for staging HCC, for determining whether HCC has metastasized, and for imaging HCC. There is also a need for better treatment of HCC.

### SUMMARY OF THE INVENTION

The present invention solves many needs in the art by providing nucleic acid molecules, polypeptides and antibodies thereto, variants and derivatives of the nucleic acids and polypeptides, agonists and antagonists that may be used to identify, diagnose, monitor, stage, image and treat hepatic cancer and non-cancerous disease states in hepatic; identify and monitor hepatic tissue; and identify and design agonists and antagonists of polypeptides of the invention. The invention also provides gene therapy, methods for

producing transgenic animals and cells, and methods for producing engineered hepatic tissue for treatment and research.

One aspect of the present invention relates to nucleic acid molecules that are specific to hepatic cells, hepatic tissue and/or the hepatic organ. These hepatic specific nucleic acids (HSNAs) may be a naturally occurring cDNA, genomic DNA, RNA, or a  
5 fragment of one of these nucleic acids, or may be a non-naturally occurring nucleic acid molecule. If the HSNA is genomic DNA, then the HSNA is a hepatic specific gene (HSG). If the HSNA is RNA, then it is a hepatic specific transcript encoded by a HSG. Due to alternative splicing and transcriptional modification one HSG may encode for  
10 multiple hepatic specific RNAs. In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that is specific to hepatic. More preferred is a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 410-611. In another preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-409. For the HSNA sequences listed herein,  
15 DEX0374\_001.nt.1 corresponds to SEQ ID NO: 1. For sequences with multiple splice variants, the parent sequence DEX0374\_001.nt.1, will be followed by DEX0374\_001.nt.2, etc. for each splice variant. The sequences off the corresponding peptides are listed as DEX0374\_001.aa.1, etc. For the mapping of all of the nucleotides and peptides, see the table in the Example 1 section below.

20 This aspect of the present invention also relates to nucleic acid molecules that selectively hybridize or exhibit substantial sequence similarity to nucleic acid molecules encoding a Hepatic Specific Protein (HSP), or that selectively hybridize or exhibit substantial sequence similarity to a HSNA. In one embodiment of the present invention the nucleic acid molecule comprises an allelic variant of a nucleic acid molecule encoding  
25 a HSP, or an allelic variant of a HSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid sequence that encodes a HSP or a part of a nucleic acid sequence of a HSNA.

In addition, this aspect of the present invention relates to a nucleic acid molecule further comprising one or more expression control sequences controlling the transcription  
30 and/or translation of all or a part of a HSNA or the transcription and/or translation of a nucleic acid molecule that encodes all or a fragment of a HSP.

Another aspect of the present invention relates to vectors and/or host cells comprising a nucleic acid molecule of this invention. In a preferred embodiment, the

nucleic acid molecule of the vector and/or host cell encodes all or a fragment of a HSP. In another preferred embodiment, the nucleic acid molecule of the vector and/or host cell comprises all or a part of a HSNA. Vectors and host cells of the present invention are useful in the recombinant production of polypeptides, particularly HSPs of the present invention.

Another aspect of the present invention relates to polypeptides encoded by a nucleic acid molecule of this invention. The polypeptide may comprise either a fragment or a full-length protein. In a preferred embodiment, the polypeptide is a HSP. However, this aspect of the present invention also relates to mutant proteins (muteins) of HSPs, fusion proteins of which a portion is a HSP, and proteins and polypeptides encoded by allelic variants of a HSNA as provided herein.

Another aspect of the present invention relates to antibodies and other binders that specifically binds to a polypeptide of the instant invention. Accordingly antibodies or binders of the present specifically bind to HSPs, muteins, fusion proteins, and/or homologous proteins or a polypeptides encoded by allelic variants of an HSNA as provided herein.

Another aspect of the present invention relates to agonists and antagonists of the nucleic acid molecules and polypeptides of this invention. The agonists and antagonists of the instant invention may be used to treat hepatic cancer and non-cancerous disease states in hepatic and to produce engineered hepatic tissue.

Another aspect of the present invention relates to methods for using the nucleic acid molecules to detect or amplify nucleic acid molecules that have similar or identical nucleic acid sequences compared to the nucleic acid molecules described herein. Such methods are useful in identifying, diagnosing, monitoring, staging, imaging and treating hepatic cancer and non-cancerous disease states in hepatic. Such methods are also useful in identifying and/or monitoring hepatic tissue. In addition, measurement of levels of one or more of the nucleic acid molecules of this invention may be useful for diagnostics as part of panel in combination with known other markers, particularly those described in the hepatic cancer background section above.

Another aspect of the present invention relates to use of the nucleic acid molecules of this invention in gene therapy, for producing transgenic animals and cells, and for producing engineered hepatic tissue for treatment and research.

Another aspect of the present invention relates to methods for detecting polypeptides this invention, preferably using antibodies thereto. Such methods are useful to identify, diagnose, monitor, stage, image and treat hepatic cancer and non-cancerous disease states in hepatic. In addition, measurement of levels of one or more of the

5 polypeptides of this invention may be useful to identify, diagnose, monitor, stage, image hepatic cancer in combination with known other markers, particularly those described in the hepatic cancer background section above. The polypeptides of the present invention can also be used to identify and/or monitor hepatic tissue, and to produce engineered hepatic tissue.

10 Yet another aspect of the present invention relates to a computer readable means of storing the nucleic acid and amino acid sequences of the invention. The records of the computer readable means can be accessed for reading and displaying of sequences for comparison, alignment and ordering of the sequences of the invention to other sequences. In addition, the computer records regarding the nucleic acid and/or amino acid sequences

15 and/or measurements of their levels may be used alone or in combination with other markers to diagnose hepatic related diseases.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions and General Techniques

Unless otherwise defined herein, scientific and technical terms used in connection

20 with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid

25 chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. *See, e.g., Sambrook et al., Molecular Cloning: A*

30 *Laboratory Manual*, 2d ed., Cold Spring Harbor Laboratory Press (1989) and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 3d ed., Cold Spring Harbor Press (2001); Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing Associates



(1992, and Supplements to 2000); Ausubel *et al.*, Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology – 4<sup>th</sup> Ed., Wiley & Sons (1999); Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1990); and Harlow and Lane, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1999).

Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

A “nucleic acid molecule” of this invention refers to a polymeric form of nucleotides and includes both sense and antisense strands of RNA, cDNA, genomic DNA, and synthetic forms and mixed polymers of the above. A nucleotide refers to a ribonucleotide, deoxynucleotide or a modified form of either type of nucleotide. A “nucleic acid molecule” as used herein is synonymous with “nucleic acid” and “polynucleotide.” The term “nucleic acid molecule” usually refers to a molecule of at least 10 bases in length, unless otherwise specified. The term includes single and double stranded forms of DNA. In addition, a polynucleotide may include either or both naturally occurring and modified nucleotides linked together by naturally occurring and/or non-naturally occurring nucleotide linkages.

Nucleotides are represented by single letter symbols in nucleic acid molecule sequences. The following table lists symbols identifying nucleotides or groups of nucleotides which may occupy the symbol position on a nucleic acid molecule. See Nomenclature Committee of the International Union of Biochemistry (NC-IUB), Nomenclature for incompletely specified bases in nucleic acid sequences, Recommendations 1984., *Eur J Biochem.* 150(1):1-5 (1985).

Symbol	Meaning	Group/Origin of Designation	Complementary Symbol
a	a	Adenine	t/u
g	g	Guanine	c
c	c	Cytosine	g

t	t	Thymine	a
u	u	Uracil	a
r	g or a	puRine	y
y	t/u or c	pYrimidine	r
m	a or c	aMino	k
k	g or t/u	Keto	m
s	g or c	Strong interactions 3H-bonds	w
w	a or t/u	Weak interactions 2H-bonds	s
b	g or c or t/u	not a	v
d	a or g or t/u	not c	h
h	a or c or t/u	not g	d
v	a or g or c	not t, not u	b
n	a or g or c or t/u, unknown, or other	aNy	n

The nucleic acid molecules may be modified chemically or biochemically or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those of skill in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, etc.), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen, etc.), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids, etc.) The term “nucleic acid molecule” also includes any topological conformation, including single-stranded, double-stranded, partially duplexed, triplexed, hairpinned, circular and padlocked conformations. Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

A “gene” is defined as a nucleic acid molecule that comprises a nucleic acid sequence that encodes a polypeptide and the expression control sequences that surround the nucleic acid sequence that encodes the polypeptide. For instance, a gene may comprise a promoter, one or more enhancers, a nucleic acid sequence that encodes a polypeptide, downstream regulatory sequences and, possibly, other nucleic acid sequences involved in regulation of the expression of an RNA. As is well known in the art, eukaryotic genes usually contain both exons and introns. The term “exon” refers to a nucleic acid sequence found in genomic DNA that is bioinformatically predicted and/or

experimentally confirmed to contribute contiguous sequence to a mature mRNA transcript. The term “intron” refers to a nucleic acid sequence found in genomic DNA that is predicted and/or confirmed to not contribute to a mature mRNA transcript, but rather to be “spliced out” during processing of the transcript.

5           A nucleic acid molecule or polypeptide is “derived” from a particular species if the nucleic acid molecule or polypeptide has been isolated from the particular species, or if the nucleic acid molecule or polypeptide is homologous to a nucleic acid molecule or polypeptide isolated from a particular species.

          An “isolated” or “substantially pure” nucleic acid or polynucleotide (*e.g.*, an RNA,  
10   DNA or a mixed polymer) is one which is substantially separated from other cellular components that naturally accompany the native polynucleotide in its natural host cell, *e.g.*, ribosomes, polymerases, or genomic sequences with which it is naturally associated. The term embraces a nucleic acid or polynucleotide that (1) has been removed from its naturally occurring environment, (2) is not associated with all or a portion of a  
15   polynucleotide in which the “isolated polynucleotide” is found in nature, (3) is operatively linked to a polynucleotide which it is not linked to in nature, (4) does not occur in nature as part of a larger sequence or (5) includes nucleotides or internucleoside bonds that are not found in nature. The term “isolated” or “substantially pure” also can be used in reference to recombinant or cloned DNA isolates, chemically synthesized polynucleotide  
20   analogs, or polynucleotide analogs that are biologically synthesized by heterologous systems. The term “isolated nucleic acid molecule” includes nucleic acid molecules that are integrated into a host cell chromosome at a heterologous site, recombinant fusions of a native fragment to a heterologous sequence, recombinant vectors present as episomes or as integrated into a host cell chromosome.

25           A “part” of a nucleic acid molecule refers to a nucleic acid molecule that comprises a partial contiguous sequence of at least 10 bases of the reference nucleic acid molecule. Preferably, a part comprises at least 15 to 20 bases of a reference nucleic acid molecule. In theory, a nucleic acid sequence of 17 nucleotides is of sufficient length to occur at random less frequently than once in the three gigabase human genome, and thus  
30   to provide a nucleic acid probe that can uniquely identify the reference sequence in a nucleic acid mixture of genomic complexity. A preferred part is one that comprises a nucleic acid sequence that can encode at least 6 contiguous amino acid sequences (fragments of at least 18 nucleotides) because they are useful in directing the expression or

synthesis of peptides that are useful in mapping the epitopes of the polypeptide encoded by the reference nucleic acid. *See, e.g., Geysen et al., Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1984); and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. A part may also comprise at least 25, 30, 35 or 40 nucleotides of a reference nucleic acid molecule, or at least 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides of a reference nucleic acid molecule. A part of a nucleic acid molecule may comprise no other nucleic acid sequences. Alternatively, a part of a nucleic acid may comprise other nucleic acid sequences from other nucleic acid molecules.

10       The term "oligonucleotide" refers to a nucleic acid molecule generally comprising a length of 200 bases or fewer. The term often refers to single-stranded deoxyribonucleotides, but it can refer as well to single-or double-stranded ribonucleotides, RNA:DNA hybrids and double-stranded DNAs, among others. Preferably, oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19 or 20 bases in length. Other preferred oligonucleotides are 25, 30, 35, 40, 45, 50, 55 or 60 bases in length. Oligonucleotides may be single-stranded, *e.g.* for use as probes or primers, or may be double-stranded, *e.g.* for use in the construction of a mutant gene. Oligonucleotides of the invention can be either sense or antisense oligonucleotides. An oligonucleotide can be derivatized or modified as discussed above for nucleic acid molecules.

20       Oligonucleotides, such as single-stranded DNA probe oligonucleotides, often are synthesized by chemical methods, such as those implemented on automated oligonucleotide synthesizers. However, oligonucleotides can be made by a variety of other methods, including in vitro recombinant DNA-mediated techniques and by expression of DNAs in cells and organisms. Initially, chemically synthesized DNAs typically are obtained without a 5' phosphate. The 5' ends of such oligonucleotides are not substrates for phosphodiester bond formation by ligation reactions that employ DNA ligases typically used to form recombinant DNA molecules. Where ligation of such oligonucleotides is desired, a phosphate can be added by standard techniques, such as those that employ a kinase and ATP. The 3' end of a chemically synthesized oligonucleotide generally has a free hydroxyl group and, in the presence of a ligase, such as T4 DNA ligase, readily will form a phosphodiester bond with a 5' phosphate of another polynucleotide, such as another oligonucleotide. As is well known, this reaction can be

prevented selectively, where desired, by removing the 5' phosphates of the other polynucleotide(s) prior to ligation.

The term "naturally occurring nucleotide" referred to herein includes naturally occurring deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "nucleotide linkages" referred to herein includes nucleotide linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoroamidate, and the like. *See e.g., LaPlanche et al. Nucl. Acids Res.* 14:9081-9093 (1986); *Stein et al. Nucl. Acids Res.* 16:3209-3221 (1988); *Zon et al. Anti-Cancer Drug Design* 6:539-568 (1991); *Zon et al., in Eckstein (ed.) Oligonucleotides and Analogues: A Practical Approach*, pp. 87-108, Oxford University Press (1991); *Uhlmann and Peyman Chemical Reviews* 90:543 (1990), and U.S. Patent No. 5,151,510, the disclosure of which is hereby incorporated by reference in its entirety.

Unless specified otherwise, the left hand end of a polynucleotide sequence in sense orientation is the 5' end and the right hand end of the sequence is the 3' end. In addition, the left hand direction of a polynucleotide sequence in sense orientation is referred to as the 5' direction, while the right hand direction of the polynucleotide sequence is referred to as the 3' direction. Further, unless otherwise indicated, each nucleotide sequence is set forth herein as a sequence of deoxyribonucleotides. It is intended, however, that the given sequence be interpreted as would be appropriate to the polynucleotide composition: for example, if the isolated nucleic acid is composed of RNA, the given sequence intends ribonucleotides, with uridine substituted for thymidine.

The term "allelic variant" refers to one of two or more alternative naturally occurring forms of a gene, wherein each gene possesses a unique nucleotide sequence. In a preferred embodiment, different alleles of a given gene have similar or identical biological properties.

The term "percent sequence identity" in the context of nucleic acid sequences refers to the residues in two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number

of different algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap or Bestfit, which are programs in Wisconsin Package Version 10.0, Genetics Computer Group (GCG), Madison, Wisconsin. FASTA, which includes, *e.g.*, the programs FASTA2  
5 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183: 63-98 (1990); Pearson, *Methods Mol. Biol.* 132: 185-219 (2000); Pearson, *Methods Enzymol.* 266: 227-258 (1996); Pearson, *J. Mol. Biol.* 276: 71-84 (1998)). Unless otherwise specified, default parameters for a particular program or algorithm are used. For instance,  
10 percent sequence identity between nucleic acid sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in GCG Version 6.1.

A reference to a nucleic acid sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid molecule having a particular  
15 sequence should be understood to encompass its complementary strand, with its complementary sequence. The complementary strand is also useful, *e.g.*, for antisense therapy, double stranded RNA (dsRNA) inhibition (RNAi), combination of triplex and antisense, hybridization probes and PCR primers.

In the molecular biology art, researchers use the terms "percent sequence identity",  
20 "percent sequence similarity" and "percent sequence homology" interchangeably. In this application, these terms shall have the same meaning with respect to nucleic acid sequences only.

The term "substantial similarity" or "substantial sequence similarity," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with  
25 appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 50%, more preferably 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95-98% of the nucleotide bases, as measured by any well known algorithm of sequence identity, such  
30 as FASTA, BLAST or Gap, as discussed above.

Alternatively, substantial similarity exists between a first and second nucleic acid sequence when the first nucleic acid sequence or fragment thereof hybridizes to an antisense strand of the second nucleic acid, under selective hybridization conditions.

Typically, selective hybridization will occur between the first nucleic acid sequence and an antisense strand of the second nucleic acid sequence when there is at least about 55% sequence identity between the first and second nucleic acid sequences— preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90% —  
 5 over a stretch of at least about 14 nucleotides, more preferably at least 17 nucleotides, even more preferably at least 20, 25, 30, 35, 40, 50, 60, 70, 80, 90 or 100 nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, solvents, the base composition of the hybridizing species, length of the complementary regions, and the number of nucleotide base mismatches  
 10 between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. “Stringent hybridization conditions” and “stringent wash conditions” in the context of nucleic acid hybridization experiments depend upon a number of different physical parameters. The most important parameters include temperature of hybridization, base composition of the nucleic acids, salt concentration and length of the nucleic acid. One  
 15 having ordinary skill in the art knows how to vary these parameters to achieve a particular stringency of hybridization. In general, “stringent hybridization” is performed at about 25°C below the thermal melting point ( $T_m$ ) for the specific DNA hybrid under a particular set of conditions. “Stringent washing” is performed at temperatures about 5°C lower than the  $T_m$  for the specific DNA hybrid under a particular set of conditions. The  $T_m$  is the  
 20 temperature at which 50% of the target sequence hybridizes to a perfectly matched probe. See Sambrook (1989), *supra*, p. 9.51.

The  $T_m$  for a particular DNA-DNA hybrid can be estimated by the formula:

$$T_m = 81.5^{\circ}\text{C} + 16.6 (\log_{10}[\text{Na}^+]) + 0.41 (\text{fraction G} + \text{C}) - 0.63 (\% \text{ formamide}) - (600/l) \text{ where } l \text{ is the length of the hybrid in base pairs.}$$

25 The  $T_m$  for a particular RNA-RNA hybrid can be estimated by the formula:

$$T_m = 79.8^{\circ}\text{C} + 18.5 (\log_{10}[\text{Na}^+]) + 0.58 (\text{fraction G} + \text{C}) + 11.8 (\text{fraction G} + \text{C})^2 - 0.35 (\% \text{ formamide}) - (820/l).$$

The  $T_m$  for a particular RNA-DNA hybrid can be estimated by the formula:

$$T_m = 79.8^{\circ}\text{C} + 18.5 (\log_{10}[\text{Na}^+]) + 0.58 (\text{fraction G} + \text{C}) + 11.8 (\text{fraction G} + \text{C})^2 - 0.50 (\% \text{ formamide}) - (820/l).$$

30 In general, the  $T_m$  decreases by 1-1.5°C for each 1% of mismatch between two nucleic acid sequences. Thus, one having ordinary skill in the art can alter hybridization and/or washing conditions to obtain sequences that have higher or lower degrees of

sequence identity to the target nucleic acid. For instance, to obtain hybridizing nucleic acids that contain up to 10% mismatch from the target nucleic acid sequence, 10-15°C would be subtracted from the calculated  $T_m$  of a perfectly matched hybrid, and then the hybridization and washing temperatures adjusted accordingly. Probe sequences may also  
5 hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

An example of stringent hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on  
10 a filter in a Southern or Northern blot or for screening a library is 50% formamide/6X SSC at 42°C for at least ten hours and preferably overnight (approximately 16 hours). Another example of stringent hybridization conditions is 6X SSC at 68°C without formamide for at least ten hours and preferably overnight. An example of moderate stringency hybridization conditions is 6X SSC at 55°C without formamide for at least ten hours and  
15 preferably overnight. An example of low stringency hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or northern blot or for screening a library is 6X SSC at 42°C for at least ten hours. Hybridization conditions to identify nucleic acid sequences that are similar but not identical can be identified by experimentally changing  
20 the hybridization temperature from 68°C to 42°C while keeping the salt concentration constant (6X SSC), or keeping the hybridization temperature and salt concentration constant (e.g. 42°C and 6X SSC) and varying the formamide concentration from 50% to 0%. Hybridization buffers may also include blocking agents to lower background. These agents are well known in the art. *See Sambrook et al. (1989), supra*, pages 8.46 and 9.46-  
25 9.58. *See also Ausubel (1992), supra, Ausubel (1999), supra, and Sambrook (2001), supra.*

Wash conditions also can be altered to change stringency conditions. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (*see Sambrook (1989), supra*, for SSC buffer). Often the high stringency wash is preceded by a low  
30 stringency wash to remove excess probe. An exemplary medium stringency wash for duplex DNA of more than 100 base pairs is 1x SSC at 45°C for 15 minutes. An exemplary low stringency wash for such a duplex is 4x SSC at 40°C for 15 minutes. In



general, signal-to-noise ratio of 2x or higher than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization.

As defined herein, nucleic acids that do not hybridize to each other under stringent conditions are still substantially similar to one another if they encode polypeptides that are substantially identical to each other. This occurs, for example, when a nucleic acid is created synthetically or recombinantly using a high codon degeneracy as permitted by the redundancy of the genetic code.

Hybridization conditions for nucleic acid molecules that are shorter than 100 nucleotides in length (*e.g.*, for oligonucleotide probes) may be calculated by the formula:

$$T_m = 81.5^{\circ}\text{C} + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\text{fraction G+C}) - (600/N),$$
 wherein N is change length and the  $[\text{Na}^+]$  is 1 M or less. *See* Sambrook (1989), *supra*, p. 11.46. For hybridization of probes shorter than 100 nucleotides, hybridization is usually performed under stringent conditions (5-10°C below the  $T_m$ ) using high concentrations (0.1-1.0 pmol/ml) of probe. *Id.* at p. 11.45. Determination of hybridization using mismatched probes, pools of degenerate probes or “guessmers,” as well as hybridization solutions and methods for empirically determining hybridization conditions are well known in the art. *See, e.g.*, Ausubel (1999), *supra*; Sambrook (1989), *supra*, pp. 11.45-11.57.

The term “digestion” or “digestion of DNA” refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes referred to herein are commercially available and their reaction conditions, cofactors and other requirements for use are known and routine to the skilled artisan. For analytical purposes, typically, 1 µg of plasmid or DNA fragment is digested with about 2 units of enzyme in about 20 µl of reaction buffer. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 µg of DNA are digested with 20 to 250 units of enzyme in proportionately larger volumes. Appropriate buffers and substrate amounts for particular restriction enzymes are described in standard laboratory manuals, such as those referenced below, and are specified by commercial suppliers. Incubation times of about 1 hour at 37°C are ordinarily used, but conditions may vary in accordance with standard procedures, the supplier’s instructions and the particulars of the reaction. After digestion, reactions may be analyzed, and fragments may be purified by electrophoresis through an agarose or polyacrylamide gel, using well known methods that are routine for those skilled in the art.

The term "ligation" refers to the process of forming phosphodiester bonds between two or more polynucleotides, which most often are double-stranded DNAs. Techniques for ligation are well known to the art and protocols for ligation are described in standard laboratory manuals and references, such as, *e.g.*, Sambrook (1989), *supra*.

5       Genome-derived "single exon probes," are probes that comprise at least part of an exon ("reference exon") and can hybridize detectably under high stringency conditions to transcript-derived nucleic acids that include the reference exon but do not hybridize detectably under high stringency conditions to nucleic acids that lack the reference exon. Single exon probes typically further comprise, contiguous to a first end of the exon  
10       portion, a first intronic and/or intergenic sequence that is identically contiguous to the exon in the genome, and may contain a second intronic and/or intergenic sequence that is identically contiguous to the exon in the genome. The minimum length of genome-derived single exon probes is defined by the requirement that the exonic portion be of sufficient length to hybridize under high stringency conditions to transcript-derived  
15       nucleic acids, as discussed above. The maximum length of genome-derived single exon probes is defined by the requirement that the probes contain portions of no more than one exon. The single exon probes may contain priming sequences not found in contiguity with the rest of the probe sequence in the genome, which priming sequences are useful for PCR and other amplification-based technologies. In another aspect, the invention is directed to  
20       single exon probes based on the HSNAs disclosed herein.

In one embodiment, the term "microarray" refers to a "nucleic acid microarray" having a substrate-bound plurality of nucleic acids, hybridization to each of the plurality of bound nucleic acids being separately detectable. The substrate can be solid or porous, planar or non-planar, unitary or distributed. Nucleic acid microarrays include all the  
25       devices so called in Schena (ed.), DNA Microarrays: A Practical Approach (Practical Approach Series), Oxford University Press (1999); *Nature Genet.* 21(1)(suppl.):1 - 60 (1999); Schena (ed.), Microarray Biochip: Tools and Technology, Eaton Publishing Company/BioTechniques Books Division (2000). Additionally, these nucleic acid microarrays include substrate-bound plurality of nucleic acids in which the plurality of  
30       nucleic acids are disposed on a plurality of beads, rather than on a unitary planar substrate, as is described, *inter alia*, in Brenner *et al.*, *Proc. Natl. Acad. Sci. USA* 97(4):1665-1670 (2000). Examples of nucleic acid microarrays may be found in U.S. Patent Nos. 6,391,623, 6,383,754, 6,383,749, 6,380,377, 6,379,897, 6,376,191, 6,372,431, 6,351,712

6,344,316, 6,316,193, 6,312,906, 6,309,828, 6,309,824, 6,306,643, 6,300,063, 6,287,850, 6,284,497, 6,284,465, 6,280,954, 6,262,216, 6,251,601, 6,245,518, 6,263,287, 6,251,601, 6,238,866, 6,228,575, 6,214,587, 6,203,989, 6,171,797, 6,103,474, 6,083,726, 6,054,274, 6,040,138, 6,083,726, 6,004,755, 6,001,309, 5,958,342, 5,952,180, 5,936,731, 5,843,655, 5,814,454, 5,837,196, 5,436,327, 5,412,087, 5,405,783, the disclosures of which are incorporated herein by reference in their entireties.

In an alternative embodiment, a "microarray" may also refer to a "peptide microarray" or "protein microarray" having a substrate-bound collection of plurality of polypeptides, the binding to each of the plurality of bound polypeptides being separately detectable. Alternatively, the peptide microarray may have a plurality of binders, including but not limited to monoclonal antibodies, polyclonal antibodies, phage display binders, yeast 2 hybrid binders, aptamers, which can specifically detect the binding of the polypeptides of this invention. The array may be based on autoantibody detection to the polypeptides of this invention, see Robinson *et al.*, *Nature Medicine* 8(3):295-301 (2002). Examples of peptide arrays may be found in WO 02/31463, WO 02/25288, WO 01/94946, WO 01/88162, WO 01/68671, WO 01/57259, WO 00/61806, WO 00/54046, WO 00/47774, WO 99/40434, WO 99/39210, WO 97/42507 and U.S. Patent Nos. 6,268,210, 5,766,960, 5,143,854, the disclosures of which are incorporated herein by reference in their entireties.

In addition, determination of the levels of the HSNA or HSP may be made in a multiplex manner using techniques described in WO 02/29109, WO 02/24959, WO 01/83502, WO01/73113, WO 01/59432, WO 01/57269, WO 99/67641, the disclosures of which are incorporated herein by reference in their entireties.

The term "mutant", "mutated", or "mutation" when applied to nucleic acid sequences means that nucleotides in a nucleic acid sequence may be inserted, deleted or changed compared to a reference nucleic acid sequence. A single alteration may be made at a locus (a point mutation) or multiple nucleotides may be inserted, deleted or changed at a single locus. In addition, one or more alterations may be made at any number of loci within a nucleic acid sequence. In a preferred embodiment of the present invention, the nucleic acid sequence is the wild type nucleic acid sequence encoding a HSP or is a HSNA. The nucleic acid sequence may be mutated by any method known in the art including those mutagenesis techniques described *infra*.

The term “error-prone PCR” refers to a process for performing PCR under conditions where the copying fidelity of the DNA polymerase is low, such that a high rate of point mutations is obtained along the entire length of the PCR product. *See, e.g., Leung et al., Technique 1: 11-15 (1989) and Caldwell et al., PCR Methods Applic. 2: 28-33*

5 (1992).

The term “oligonucleotide-directed mutagenesis” refers to a process which enables the generation of site-specific mutations in any cloned DNA segment of interest. *See, e.g., Reidhaar-Olson et al., Science 241: 53-57 (1988).*

The term “assembly PCR” refers to a process which involves the assembly of a  
10 PCR product from a mixture of small DNA fragments. A large number of different PCR reactions occur in parallel in the same vial, with the products of one reaction priming the products of another reaction.

The term “sexual PCR mutagenesis” or “DNA shuffling” refers to a method of error-prone PCR coupled with forced homologous recombination between DNA  
15 molecules of different but highly related DNA sequence *in vitro*, caused by random fragmentation of the DNA molecule based on sequence similarity, followed by fixation of the crossover by primer extension in an error-prone PCR reaction. *See, e.g., Stemmer, Proc. Natl. Acad. Sci. U.S.A. 91: 10747-10751 (1994).* DNA shuffling can be carried out between several related genes (“Family shuffling”).

The term “*in vivo* mutagenesis” refers to a process of generating random mutations  
20 in any cloned DNA of interest which involves the propagation of the DNA in a strain of bacteria such as *E. coli* that carries mutations in one or more of the DNA repair pathways. These “mutator” strains have a higher random mutation rate than that of a wild-type parent. Propagating the DNA in a mutator strain will eventually generate random  
25 mutations within the DNA.

The term “cassette mutagenesis” refers to any process for replacing a small region of a double-stranded DNA molecule with a synthetic oligonucleotide “cassette” that differs from the native sequence. The oligonucleotide often contains completely and/or partially randomized native sequence.

30 The term “recursive ensemble mutagenesis” refers to an algorithm for protein engineering (protein mutagenesis) developed to produce diverse populations of phenotypically related mutants whose members differ in amino acid sequence. This

method uses a feedback mechanism to control successive rounds of combinatorial cassette mutagenesis. *See, e.g., Arkin et al., Proc. Natl. Acad. Sci. U.S.A.* 89: 7811-7815 (1992).

The term "exponential ensemble mutagenesis" refers to a process for generating combinatorial libraries with a high percentage of unique and functional mutants, wherein  
5 small groups of residues are randomized in parallel to identify, at each altered position, amino acids which lead to functional proteins. *See, e.g., Delegrave et al., Biotechnology Research* 11: 1548-1552 (1993); Arnold, *Current Opinion in Biotechnology* 4: 450-455 (1993).

"Operatively linked" expression control sequences refers to a linkage in which the  
10 expression control sequence is either contiguous with the gene of interest to control the gene of interest, or acts in *trans* or at a distance to control the gene of interest.

The term "expression control sequence" as used herein refers to polynucleotide sequences which are necessary to affect the expression of coding sequences to which they are operatively linked. Expression control sequences are sequences which control the  
15 transcription, post-transcriptional events and translation of nucleic acid sequences. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*e.g.,* ribosome binding sites); sequences that enhance  
20 protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression, and can also include additional  
25 components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which  
30 additional DNA segments may be ligated. Other vectors include cosmids, bacterial artificial chromosomes (BAC) and yeast artificial chromosomes (YAC). Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Viral vectors that infect bacterial cells are referred to as bacteriophages. Certain

vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication). Other vectors can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression vectors”). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include other forms of expression vectors that serve equivalent functions.

The term “recombinant host cell” (or simply “host cell”), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term “host cell” as used herein.

As used herein, the phrase “open reading frame” and the equivalent acronym “ORF” refers to that portion of a transcript-derived nucleic acid that can be translated in its entirety into a sequence of contiguous amino acids. As so defined, an ORF has length, measured in nucleotides, exactly divisible by 3. As so defined, an ORF need not encode the entirety of a natural protein.

As used herein, the phrase “ORF-encoded peptide” refers to the predicted or actual translation of an ORF.

As used herein, the phrase “degenerate variant” of a reference nucleic acid sequence is meant to be inclusive of all nucleic acid sequences that can be directly translated, using the standard genetic code, to provide an amino acid sequence identical to that translated from the reference nucleic acid sequence.

The term “polypeptide” encompasses both naturally occurring and non-naturally occurring proteins and polypeptides, as well as polypeptide fragments and polypeptide mutants, derivatives and analogs thereof. A polypeptide may be monomeric or polymeric. Further, a polypeptide may comprise a number of different modules within a single

polypeptide each of which has one or more distinct activities. A preferred polypeptide in accordance with the invention comprises a HSP encoded by a nucleic acid molecule of the instant invention, or a fragment, mutant, analog and derivative thereof.

The term "isolated protein" or "isolated polypeptide" is a protein or polypeptide  
5 that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is free of other proteins from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated"  
10 from its naturally associated components. A polypeptide or protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

A protein or polypeptide is "substantially pure," "substantially homogeneous" or "substantially purified" when at least about 60% to 75% of a sample exhibits a single  
15 species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be determined by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample,  
20 followed by visualizing a single polypeptide band upon staining the gel with a stain well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The term "fragment" when used herein with respect to polypeptides of the present invention refers to a polypeptide that has an amino-terminal and/or carboxy-terminal  
25 deletion compared to a full-length HSP. In a preferred embodiment, the fragment is a contiguous sequence in which the amino acid sequence of the fragment is identical to the corresponding positions in the naturally occurring polypeptide. Fragments typically are at least 5, 6, 7, 8, 9 or 10 amino acids long, preferably at least 12, 14, 16 or 18 amino acids long, more preferably at least 20 amino acids long, more preferably at least 25, 30, 35, 40  
30 or 45, amino acids, even more preferably at least 50 or 60 amino acids long, and even more preferably at least 70 amino acids long.

A "derivative" when used herein with respect to polypeptides of the present invention refers to a polypeptide which is substantially similar in primary structural

sequence to a HSP but which include, *e.g.*, *in vivo* or *in vitro* chemical and biochemical modifications that are not found in the HSP. Such modifications include, for example, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Other modification include, *e.g.*, labeling with radionuclides, and various enzymatic modifications, as will be readily appreciated by those skilled in the art. A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes are well known in the art, and include radioactive isotopes such as  $^{125}\text{I}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$  and  $^3\text{H}$ , ligands which bind to labeled antiligands (*e.g.*, antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required, ease of conjugation with the primer, stability requirements, and available instrumentation. Methods for labeling polypeptides are well known in the art. *See* Ausubel (1992), *supra*; Ausubel (1999), *supra*.

The term "fusion protein" refers to polypeptides of the present invention coupled to a heterologous amino acid sequences. Fusion proteins are useful because they can be constructed to contain two or more desired functional elements from two or more different proteins. A fusion protein comprises at least 10 contiguous amino acids from a polypeptide of interest, more preferably at least 20 or 30 amino acids, even more preferably at least 40, 50 or 60 amino acids, yet more preferably at least 75, 100 or 125 amino acids. Fusion proteins can be produced recombinantly by constructing a nucleic acid sequence that encodes the polypeptide or a fragment thereof in frame with a nucleic acid sequence encoding a different protein or peptide and then expressing the fusion protein. Alternatively, a fusion protein can be produced chemically by crosslinking the polypeptide or a fragment thereof to another protein.



The term "analog" refers to both polypeptide analogs and non-peptide analogs. The term "polypeptide analog" as used herein refers to a polypeptide that is comprised of a segment of at least 25 amino acids that has substantial identity to a portion of an amino acid sequence but which contains non-natural amino acids or non-natural inter-residue bonds. In a preferred embodiment, the analog has the same or similar biological activity as the native polypeptide. Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the naturally occurring sequence. Analogs typically are at least 20 amino acids long, preferably at least 50 amino acids long or longer, and can often be as long as a full-length naturally occurring polypeptide.

The term "non-peptide analog" refers to a compound with properties that are analogous to those of a reference polypeptide. A non-peptide compound may also be termed a "peptide mimetic" or a "peptidomimetic." Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to useful peptides may be used to produce an equivalent effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a desired biochemical property or pharmacological activity), but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH<sub>2</sub>NH--, --CH<sub>2</sub>S--, --CH<sub>2</sub>-CH<sub>2</sub>--, --CH=CH--(cis and trans), --COCH<sub>2</sub>--, --CH(OH)CH<sub>2</sub>--, and --CH<sub>2</sub>SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo *et al.*, *Ann. Rev. Biochem.* 61:387-418 (1992)). For example, one may add internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

The term "mutant" or "mutein" when referring to a polypeptide of the present invention relates to an amino acid sequence containing substitutions, insertions or deletions of one or more amino acids compared to the amino acid sequence of a HSP. A mutein may have one or more amino acid point substitutions, in which a single amino acid at a position has been changed to another amino acid, one or more insertions and/or deletions, in which one or more amino acids are inserted or deleted, respectively, in the

sequence of the naturally occurring protein, and/or truncations of the amino acid sequence at either or both the amino or carboxy termini. Further, a mutein may have the same or different biological activity as the naturally occurring protein. For instance, a mutein may have an increased or decreased biological activity. A mutein has at least 50% sequence similarity to the wild type protein, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are muteins having 80%, 85% or 90% sequence similarity to a HSP. In an even more preferred embodiment, a mutein exhibits 95% sequence identity, even more preferably 97%, even more preferably 98% and even more preferably 99%. Sequence similarity may be measured by any common sequence analysis algorithm, such as GAP or BESTFIT or other variation Smith-Waterman alignment. *See*, T. F. Smith and M. S. Waterman, J. Mol. Biol. 147:195-197 (1981) and W.R. Pearson, Genomics 11:635-650 (1991).

Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinity or enzymatic activity, and (5) confer or modify other physicochemical or functional properties of such analogs. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. In a preferred embodiment, the amino acid substitutions are moderately conservative substitutions or conservative substitutions. In a more preferred embodiment, the amino acid substitutions are conservative substitutions. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not tend to disrupt a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in Creighton (ed.), Proteins, Structures and Molecular Principles, W. H. Freeman and Company (1984); Branden *et al.* (ed.), Introduction to Protein Structure, Garland Publishing (1991); Thornton *et al.*, *Nature* 354:105-106 (1991).

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. *See* Golub *et al.* (eds.), Immunology - A Synthesis 2<sup>nd</sup> Ed., Sinauer Associates (1991). Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as  $\alpha$ -,  $\alpha$ -disubstituted amino acids, N-alkyl amino acids,

and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include:

4-hydroxyproline,  $\gamma$ -carboxyglutamate,  $\epsilon$ -N,N,N-trimethyllysine,  $\epsilon$ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine,

- 5 5-hydroxylysine, s-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the lefthand direction is the amino terminal direction and the right hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

- By "homology" or "homologous" when referring to a polypeptide of the present invention it is meant polypeptides from different organisms with a similar sequence to the encoded amino acid sequence of a HSP and a similar biological activity or function. Although two polypeptides are said to be "homologous," this does not imply that there is necessarily an evolutionary relationship between the polypeptides. Instead, the term "homologous" is defined to mean that the two polypeptides have similar amino acid sequences and similar biological activities or functions. In a preferred embodiment, a homologous polypeptide is one that exhibits 50% sequence similarity to HSP, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are homologous polypeptides that exhibit 80%, 85% or 90% sequence similarity to a HSP. In a yet more preferred embodiment, a homologous polypeptide exhibits 95%, 97%, 98% or 99% sequence similarity.

- When "sequence similarity" is used in reference to polypeptides, it is recognized that residue positions that are not identical often differ by conservative amino acid substitutions. In a preferred embodiment, a polypeptide that has "sequence similarity" comprises conservative or moderately conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (*e.g.*, charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. *See, e.g., Pearson, Methods Mol. Biol.* 24: 307-31 (1994).

For instance, the following six groups each contain amino acids that are conservative substitutions for one another:

- 1) Serine (S), Threonine (T);
- 2) Aspartic Acid (D), Glutamic Acid (E);
- 5 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Alanine (A), Valine (V), and
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.*, *Science* 256: 1443-45 (1992). A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG contains programs such as "Gap" and "Bestfit" which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. *See, e.g.*, GCG Version 6.1. Other programs include FASTA, discussed *supra*.

A preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn. *See, e.g.*, Altschul *et al.*, *J. Mol. Biol.* 215: 403-410 (1990); Altschul *et al.*, *Nucleic Acids Res.* 25:3389-402 (1997). Preferred parameters for blastp are:

Expectation value:	10 (default)
Filter:	seg (default)
Cost to open a gap:	11 (default)
30 Cost to extend a gap:	1 (default)
Max. alignments:	100 (default)
Word size:	11 (default)
No. of descriptions:	100 (default)

Penalty Matrix: BLOSUM62

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number of different organisms, it is preferable to compare amino acid sequences.

Algorithms other than blastp for database searching using amino acid sequences are known in the art. For instance, polypeptide sequences can be compared using FASTA, a program in GCG Version 6.1. FASTA (*e.g.*, FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (1990), *supra*; Pearson (2000), *supra*. For example, percent sequence identity between amino acid sequences can be determined using FASTA with its default or recommended parameters (a word size of 2 and the PAM250 scoring matrix), as provided in GCG Version 6.1.

An “antibody” refers to an intact immunoglobulin, or to an antigen-binding portion thereof that competes with the intact antibody for specific binding to a molecular species, *e.g.*, a polypeptide of the instant invention. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies.

Antigen-binding portions include, *inter alia*, Fab, Fab', F(ab')<sub>2</sub>, Fv, dAb, and

complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. A Fab fragment is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab')<sub>2</sub> fragment is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consists of the VH and CH1 domains; a Fv fragment consists of the VL and VH domains of a single arm of an antibody; and a dAb fragment consists of a VH domain. *See, e.g.*, Ward *et al.*, *Nature* 341: 544-546 (1989).

By “bind specifically” and “specific binding” as used herein it is meant the ability of the antibody to bind to a first molecular species in preference to binding to other molecular species with which the antibody and first molecular species are admixed. An antibody is said specifically to “recognize” a first molecular species when it can bind specifically to that first molecular species.

A single-chain antibody (scFv) is an antibody in which VL and VH regions are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain. *See, e.g., Bird et al., Science* 242: 423-426 (1988); Huston *et al., Proc. Natl. Acad. Sci. USA* 85: 5879-5883 (1988). Diabodies are bivalent, bispecific  
5 antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites. *See e.g., Holliger et al., Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993); Poljak *et al., Structure* 2: 1121-1123 (1994). One or more CDRs  
10 may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest. A chimeric antibody is an antibody  
15 that contains one or more regions from one antibody and one or more regions from one or more other antibodies.

An antibody may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally occurring immunoglobulin has two identical binding sites, a single-chain  
20 antibody or Fab fragment has one binding site, while a "bispecific" or "bifunctional" antibody has two different binding sites.

An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a  
25 cell from a different species, or (4) does not occur in nature. It is known that purified proteins, including purified antibodies, may be stabilized with non-naturally-associated components. The non-naturally-associated component may be a protein, such as albumin (*e.g., BSA*) or a chemical such as polyethylene glycol (PEG).

A "neutralizing antibody" or "an inhibitory antibody" is an antibody that inhibits  
30 the activity of a polypeptide or blocks the binding of a polypeptide to a ligand that normally binds to it. An "activating antibody" is an antibody that increases the activity of a polypeptide.

The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is less than 1  $\mu$ M, preferably less than 100 nM and most preferably less than 10 nM.

The term "patient" includes human and veterinary subjects.

Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

The term "hepatic specific" refers to a nucleic acid molecule or polypeptide that is expressed predominantly in the hepatic as compared to other tissues in the body. In a preferred embodiment, a "hepatic specific" nucleic acid molecule or polypeptide is detected at a level that is 1.5-fold higher than any other tissue in the body. In a more preferred embodiment, the "hepatic specific" nucleic acid molecule or polypeptide is detected at a level that is 2-fold higher than any other tissue in the body, more preferably 5-fold higher, still more preferably at least 10-fold, 15-fold, 20-fold, 25-fold, 50-fold or 100-fold higher than any other tissue in the body. Nucleic acid molecule levels may be measured by nucleic acid hybridization, such as Northern blot hybridization, or quantitative PCR. Polypeptide levels may be measured by any method known to accurately quantitate protein levels, such as Western blot analysis.

#### Nucleic Acid Molecules, Regulatory Sequences, Vectors, Host Cells and Recombinant Methods of Making Polypeptides

##### *Nucleic Acid Molecules*

One aspect of the invention provides isolated nucleic acid molecules that are specific to the hepatic or to hepatic cells or tissue or that are derived from such nucleic acid molecules. These isolated hepatic specific nucleic acids (HSNAs) may comprise cDNA genomic DNA, RNA, or a combination thereof, a fragment of one of these nucleic acids, or may be a non-naturally occurring nucleic acid molecule. A HSNA may be derived from an animal. In a preferred embodiment, the HSNA is derived from a human or other mammal. In a more preferred embodiment, the HSNA is derived from a human

or other primate. In an even more preferred embodiment, the HSNA is derived from a human.

In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that is specific to hepatic, a hepatic-specific polypeptide (HSP). In a more preferred  
5 embodiment, the nucleic acid molecule encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 410-611. In another highly preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-409.

Nucleotide sequences of the instantly-described nucleic acid molecules were determined by assembling several DNA molecules from either public or proprietary databases. Some  
10 of the underlying DNA sequences are the result, directly or indirectly, of at least one enzymatic polymerization reaction (*e.g.*, reverse transcription and/or polymerase chain reaction) using an automated sequencer (such as the MegaBACE™ 1000, Amersham Biosciences, Sunnyvale, CA, USA).

Nucleic acid molecules of the present invention may also comprise sequences that  
15 selectively hybridizes to a nucleic acid molecule encoding a HSNA or a complement or antisense thereof. The hybridizing nucleic acid molecule may or may not encode a polypeptide or may or may not encode a HSP. However, in a preferred embodiment, the hybridizing nucleic acid molecule encodes a HSP. In a more preferred embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid  
20 molecule or the antisense sequence of a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 410-611. In an even more preferred embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 1-409 or the antisense sequence thereof. Preferably, the nucleic acid molecule selectively hybridizes to  
25 a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a HSP under low stringency conditions. More preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a HSP under moderate stringency conditions. Most preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense  
30 sequence of a nucleic acid molecule encoding a HSP under high stringency conditions. In a preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:



410-611. In a more preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule comprising a nucleic acid sequence selected from SEQ ID NO: 1-409.

5           Nucleic acid molecules of the present invention may also comprise nucleic acid sequences that exhibit substantial sequence similarity to a nucleic acid encoding a HSP or a complement of the encoding nucleic acid molecule. In this embodiment, it is preferred that the nucleic acid molecule exhibit substantial sequence similarity to a nucleic acid molecule encoding human HSP. More preferred is a nucleic acid molecule exhibiting  
10           substantial sequence similarity to a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 410-611. By substantial sequence similarity it is meant a nucleic acid molecule having at least 60% sequence identity with a nucleic acid molecule encoding a HSP, such as a polypeptide having an amino acid sequence of SEQ ID NO: 410-611, more preferably at least 70%, even more preferably at least 80% and  
15           even more preferably at least 85%. In a more preferred embodiment, the similar nucleic acid molecule is one that has at least 90% sequence identity with a nucleic acid molecule encoding a HSP, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%. Most preferred in this embodiment is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or  
20           99.9% sequence identity with a nucleic acid molecule encoding a HSP.

          The nucleic acid molecules of the present invention are also inclusive of those exhibiting substantial sequence similarity to a HSNA or its complement. In this embodiment, it is preferred that the nucleic acid molecule exhibit substantial sequence similarity to a nucleic acid molecule having a nucleic acid sequence of SEQ ID NO: 1-  
25           409. By substantial sequence similarity it is meant a nucleic acid molecule that has at least 60% sequence identity with a HSNA, such as one having a nucleic acid sequence of SEQ ID NO: 1-409, more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85%. More preferred is a nucleic acid molecule that has at least 90% sequence identity with a HSNA, more preferably at least 95%, more preferably  
30           at least 97%, even more preferably at least 98%, and still more preferably at least 99%. Most preferred is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a HSNA.

Nucleic acid molecules that exhibit substantial sequence similarity are inclusive of sequences that exhibit sequence identity over their entire length to a HSNA or to a nucleic acid molecule encoding a HSP, as well as sequences that are similar over only a part of its length. In this case, the part is at least 50 nucleotides of the HSNA or the nucleic acid molecule encoding a HSP, preferably at least 100 nucleotides, more preferably at least 150 or 200 nucleotides, even more preferably at least 250 or 300 nucleotides, still more preferably at least 400 or 500 nucleotides.

The substantially similar nucleic acid molecule may be a naturally occurring one that is derived from another species, especially one derived from another primate, wherein the similar nucleic acid molecule encodes an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 410-611 or demonstrates significant sequence identity to the nucleotide sequence of SEQ ID NO: 1-409. The similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule from a human, when the HSNA is a member of a gene family. The similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule derived from a non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, hamster, cow, horse and pig; and wild animals, *e.g.*, monkey, fox, lions, tigers, bears, giraffes, zebras, etc. The substantially similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule derived from a non-mammalian species, such as birds or reptiles. The naturally occurring substantially similar nucleic acid molecule may be isolated directly from humans or other species. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by random mutation of a nucleic acid molecule. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by directed mutation of a HSNA. In a preferred embodiment, the substantially similar nucleic acid molecule is an HSNA.

The nucleic acid molecules of the present invention are also inclusive of allelic variants of a HSNA or a nucleic acid encoding a HSP. For example, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes and the sequence determined from one individual of a species may differ from other allelic forms present within the population. More than 1.4 million SNPs have already identified in the human genome, International Human Genome Sequencing Consortium, *Nature* 409: 860-921 (2001) – Variants with small deletions and insertions of more than a single nucleotide are

also found in the general population, and often do not alter the function of the protein. In addition, amino acid substitutions occur frequently among natural allelic variants, and often do not substantially change protein function.

In a preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that encodes a HSP. In a more preferred embodiment, the gene is transcribed into an mRNA that encodes a HSP comprising an amino acid sequence of SEQ ID NO: 410-611. In another preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that is a HSNA. In a more preferred embodiment, the gene is transcribed into an mRNA that comprises the nucleic acid sequence of SEQ ID NO: 1-409. Also preferred is that the allelic variant is a naturally occurring allelic variant in the species of interest, particularly human.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences comprising a part of a nucleic acid sequence of the instant invention. The part may or may not encode a polypeptide, and may or may not encode a polypeptide that is a HSP. In a preferred embodiment, the part encodes a HSP. In one embodiment, the nucleic acid molecule comprises a part of a HSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that hybridizes or exhibits substantial sequence similarity to a HSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that is an allelic variant of a HSNA. In yet another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that encodes a HSP. A part comprises at least 10 nucleotides, more preferably at least 15, 17, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides. The maximum size of a nucleic acid part is one nucleotide shorter than the sequence of the nucleic acid molecule encoding the full-length protein.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences that encode fusion proteins, homologous proteins, polypeptide fragments, muteins and polypeptide analogs, as described *infra*.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences containing modifications of the native nucleic acid molecule. Examples of such modifications include, but are not limited to, nonnative internucleoside bonds, post-synthetic modifications or altered nucleotide analogues. One having ordinary skill in the art would recognize that the type of modification that may be made will depend upon the intended use of the nucleic acid molecule. For instance, when the nucleic acid molecule is

used as a hybridization probe, the range of such modifications will be limited to those that permit sequence-discriminating base pairing of the resulting nucleic acid. When used to direct expression of RNA or protein *in vitro* or *in vivo*, the range of such modifications will be limited to those that permit the nucleic acid to function properly as a polymerization substrate. When the isolated nucleic acid is used as a therapeutic agent, the modifications will be limited to those that do not confer toxicity upon the isolated nucleic acid.

Accordingly, in one embodiment, a nucleic acid molecule may include nucleotide analogues that incorporate labels that are directly detectable, such as radiolabels or fluorophores, or nucleotide analogues that incorporate labels that can be visualized in a subsequent reaction, such as biotin or various haptens. The labeled nucleic acid molecules are particularly useful as hybridization probes.

Common radiolabeled analogues include those labeled with  $^{33}\text{P}$ ,  $^{32}\text{P}$ , and  $^{35}\text{S}$ , such as  $\alpha$ - $^{32}\text{P}$ -dATP,  $\alpha$ - $^{32}\text{P}$ -dCTP,  $\alpha$ - $^{32}\text{P}$ -dGTP,  $\alpha$ - $^{32}\text{P}$ -dTTP,  $\alpha$ - $^{32}\text{P}$ -3'dATP,  $\alpha$ - $^{32}\text{P}$ -ATP,  $\alpha$ - $^{32}\text{P}$ -CTP,  $\alpha$ - $^{32}\text{P}$ -GTP,  $\alpha$ - $^{32}\text{P}$ -UTP,  $\alpha$ - $^{35}\text{S}$ -dATP,  $\gamma$ - $^{35}\text{S}$ -GTP,  $\gamma$ - $^{33}\text{P}$ -dATP, and the like.

Commercially available fluorescent nucleotide analogues readily incorporated into the nucleic acids of the present invention include Cy3-dCTP, Cy3-dUTP, Cy5-dCTP, Cy3-dUTP (Amersham Biosciences, Piscataway, New Jersey, USA), fluorescein-12-dUTP, tetramethylrhodamine-6-dUTP, Texas Red®-5-dUTP, Cascade Blue®-7-dUTP, BODIPY® FL-14-dUTP, BODIPY® TMR-14-dUTP, BODIPY® TR-14-dUTP, Rhodamine Green™-5-dUTP, Oregon Green® 488-5-dUTP, Texas Red®-12-dUTP, BODIPY® 630/650-14-dUTP, BODIPY® 650/665-14-dUTP, Alexa Fluor® 488-5-dUTP, Alexa Fluor® 532-5-dUTP, Alexa Fluor® 568-5-dUTP, Alexa Fluor® 594-5-dUTP, Alexa Fluor® 546-14-dUTP, fluorescein-12-UTP, tetramethylrhodamine-6-UTP, Texas Red®-5-UTP, Cascade Blue®-7-UTP, BODIPY® FL-14-UTP, BODIPY® TMR-14-UTP, BODIPY® TR-14-UTP, Rhodamine Green™-5-UTP, Alexa Fluor® 488-5-UTP, Alexa Fluor® 546-14-UTP (Molecular Probes, Inc. Eugene, OR, USA). One may also custom synthesize nucleotides having other fluorophores. See Henegariu *et al.*, *Nature Biotechnol.* 18: 345-348 (2000).

Haptens that are commonly conjugated to nucleotides for subsequent labeling include biotin (biotin-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA; biotin-21-UTP, biotin-21-dUTP, Clontech Laboratories, Inc., Palo Alto, CA, USA), digoxigenin (DIG-11-dUTP, alkali labile, DIG-11-UTP, Roche Diagnostics Corp.,

Indianapolis, IN, USA), and dinitrophenyl (dinitrophenyl-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA).

Nucleic acid molecules of the present invention can be labeled by incorporation of labeled nucleotide analogues into the nucleic acid. Such analogues can be incorporated by enzymatic polymerization, such as by nick translation, random priming, polymerase chain reaction (PCR), terminal transferase tailing, and end-filling of overhangs, for DNA molecules, and *in vitro* transcription driven, *e.g.*, from phage promoters, such as T7, T3, and SP6, for RNA molecules. Commercial kits are readily available for each such labeling approach. Analogues can also be incorporated during automated solid phase chemical synthesis. Labels can also be incorporated after nucleic acid synthesis, with the 5' phosphate and 3' hydroxyl providing convenient sites for post-synthetic covalent attachment of detectable labels.

Other post-synthetic approaches also permit internal labeling of nucleic acids. For example, fluorophores can be attached using a cisplatin reagent that reacts with the N7 of guanine residues (and, to a lesser extent, adenine bases) in DNA, RNA, and Peptide Nucleic Acids (PNA) to provide a stable coordination complex between the nucleic acid and fluorophore label (Universal Linkage System) (available from Molecular Probes, Inc., Eugene, OR, USA and Amersham Pharmacia Biotech, Piscataway, NJ, USA); *see Alers et al., Genes, Chromosomes & Cancer* 25: 301- 305 (1999); Jelsma *et al., J. NIH Res.* 5: 82 (1994); Van Belkum *et al., BioTechniques* 16: 148-153 (1994). Alternatively, nucleic acids can be labeled using a disulfide-containing linker (FastTag™ Reagent, Vector Laboratories, Inc., Burlingame, CA, USA) that is photo- or thermally coupled to the target nucleic acid using aryl azide chemistry; after reduction, a free thiol is available for coupling to a hapten, fluorophore, sugar, affinity ligand, or other marker.

One or more independent or interacting labels can be incorporated into the nucleic acid molecules of the present invention. For example, both a fluorophore and a moiety that in proximity thereto acts to quench fluorescence can be included to report specific hybridization through release of fluorescence quenching or to report exonucleotidic excision. *See, e.g., Tyagi et al., Nature Biotechnol.* 14: 303-308 (1996); Tyagi *et al., Nature Biotechnol.* 16: 49-53 (1998); Sokol *et al., Proc. Natl. Acad. Sci. USA* 95: 11538-11543 (1998); Kostrikis *et al., Science* 279: 1228-1229 (1998); Marras *et al., Genet. Anal.* 14: 151-156 (1999); Holland *et al., Proc. Natl. Acad. Sci. USA* 88: 7276-7280 (1991); Heid *et al., Genome Res.* 6(10): 986-94 (1996); Kuimelis *et al.,*

*Nucleic Acids Symp. Ser.* (37): 255-6 (1997); and U.S. Patent Nos. 5,846,726, 5,925,517, 5,925,517, 5,723,591 and 5,538,848, the disclosures of which are incorporated herein by reference in their entirety.

Nucleic acid molecules of the present invention may also be modified by altering  
5 one or more native phosphodiester internucleoside bonds to more nuclease-resistant,  
internucleoside bonds. See Hartmann *et al.* (eds.), Manual of Antisense Methodology:  
Perspectives in Antisense Science, Kluwer Law International (1999); Stein *et al.* (eds.),  
Applied Antisense Oligonucleotide Technology, Wiley-Liss (1998); Chadwick *et al.*  
(eds.), Oligonucleotides as Therapeutic Agents – Symposium No. 209, John Wiley & Son  
10 Ltd (1997). Such altered internucleoside bonds are often desired for techniques or for  
targeted gene correction, Gamper *et al.*, *Nucl. Acids Res.* 28(21): 4332-4339 (2000). For  
double stranded RNA inhibition which may utilize either natural ds RNA or ds RNA  
modified in its, sugar, phosphate or base, see Hannon, *Nature* 418(11): 244-251 (2002);  
Fire *et al.* in WO 99/32619; Tuschl *et al.* in US2002/0086356; Kruetzer *et al.* in WO  
15 00/44895, the disclosures of which are incorporated herein by reference in their entirety;.  
For circular antisense, see Kool in U.S. Patent No. 5,426,180, the disclosure of which is  
incorporated herein by reference in its entirety.

Modified oligonucleotide backbones include, without limitation,  
phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters,  
20 aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene  
phosphonates and chiral phosphonates, phosphinates, phosphoramidates including  
3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates,  
thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having  
normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity  
25 wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'.  
Representative U.S. Patents that teach the preparation of the above phosphorus-containing  
linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301;  
5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131;  
5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821;  
30 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, the disclosures of  
which are incorporated herein by reference in their entirety. In a preferred embodiment,  
the modified internucleoside linkages may be used for antisense techniques.

Other modified oligonucleotide backbones do not include a phosphorus atom, but have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH<sub>2</sub> component parts. Representative U.S. patents that teach the preparation of the above backbones include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437 and 5,677,439; the disclosures of which are incorporated herein by reference in their entireties.

In other preferred nucleic acid molecules, both the sugar and the internucleoside linkage are replaced with novel groups, such as peptide nucleic acids (PNA). In PNA compounds, the phosphodiester backbone of the nucleic acid is replaced with an amide-containing backbone, in particular by repeating N-(2-aminoethyl) glycine units linked by amide bonds. Nucleobases are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone, typically by methylene carbonyl linkages. PNA can be synthesized using a modified peptide synthesis protocol. PNA oligomers can be synthesized by both Fmoc and tBoc methods. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference in its entirety. Automated PNA synthesis is readily achievable on commercial synthesizers (*see, e.g.*, "PNA User's Guide," Rev. 2, February 1998, Perseptive Biosystems Part No. 60138, Applied Biosystems, Inc., Foster City, CA). PNA molecules are advantageous for a number of reasons. First, because the PNA backbone is uncharged, PNA/DNA and PNA/RNA duplexes have a higher thermal stability than is found in DNA/DNA and DNA/RNA duplexes. The T<sub>m</sub> of a PNA/DNA or PNA/RNA duplex is generally 1°C higher per base pair than the T<sub>m</sub> of the corresponding DNA/DNA or DNA/RNA duplex

(in 100 mM NaCl). Second, PNA molecules can also form stable PNA/DNA complexes at low ionic strength, under conditions in which DNA/DNA duplex formation does not occur. Third, PNA also demonstrates greater specificity in binding to complementary DNA because a PNA/DNA mismatch is more destabilizing than DNA/DNA mismatch. A  
5 single mismatch in mixed a PNA/DNA 15-mer lowers the  $T_m$  by 8–20°C (15°C on average). In the corresponding DNA/DNA duplexes, a single mismatch lowers the  $T_m$  by 4–16°C (11°C on average). Because PNA probes can be significantly shorter than DNA probes, their specificity is greater. Fourth, PNA oligomers are resistant to degradation by enzymes, and the lifetime of these compounds is extended both *in vivo* and *in vitro*  
10 because nucleases and proteases do not recognize the PNA polyamide backbone with nucleobase sidechains. See, e.g., Ray *et al.*, *FASEB J.* 14(9): 1041-60 (2000); Nielsen *et al.*, *Pharmacol Toxicol.* 86(1): 3-7 (2000); Larsen *et al.*, *Biochim Biophys Acta.* 1489(1): 159-66 (1999); Nielsen, *Curr. Opin. Struct. Biol.* 9(3): 353-7 (1999), and Nielsen, *Curr. Opin. Biotechnol.* 10(1): 71-5 (1999).

15 Nucleic acid molecules may be modified compared to their native structure throughout the length of the nucleic acid molecule or can be localized to discrete portions thereof. As an example of the latter, chimeric nucleic acids can be synthesized that have discrete DNA and RNA domains and that can be used for targeted gene repair and modified PCR reactions, as further described in, Misra *et al.*, *Biochem.* 37: 1917-1925  
20 (1998); and Finn *et al.*, *Nucl. Acids Res.* 24: 3357-3363 (1996), and U.S. Patent Nos. 5,760,012 and 5,731,181, the disclosures of which are incorporated herein by reference in their entireties.

Unless otherwise specified, nucleic acid molecules of the present invention can include any topological conformation appropriate to the desired use; the term thus  
25 explicitly comprehends, among others, single-stranded, double-stranded, triplexed, quadruplexed, partially double-stranded, partially-triplexed, partially-quadruplexed, branched, hairpinned, circular, and padlocked conformations. Padlock conformations and their utilities are further described in Banér *et al.*, *Curr. Opin. Biotechnol.* 12: 11-15  
(2001); Escude *et al.*, *Proc. Natl. Acad. Sci. USA* 14: 96(19):10603-7 (1999); and Nilsson  
30 *et al.*, *Science* 265(5181): 2085-8 (1994). Triplex and quadruplex conformations, and their utilities, are reviewed in Praseuth *et al.*, *Biochim. Biophys. Acta.* 1489(1): 181-206 (1999); Fox, *Curr. Med. Chem.* 7(1): 17-37 (2000); Kochetkova *et al.*, *Methods Mol. Biol.*



130: 189-201 (2000); Chan *et al.*, *J. Mol. Med.* 75(4): 267-82 (1997); Rowley *et al.*, *Mol Med* 5(10): 693-700 (1999); Kool, *Annu Rev Biophys Biomol Struct.* 25: 1-28 (1996).

*Methods for Using Nucleic Acid Molecules as Probes and Primers*

5       The isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize, and quantify hybridizing nucleic acids in, and isolate hybridizing nucleic acids from, both genomic and transcript-derived nucleic acid samples. When free in solution, such probes are typically, but not invariably, detectably labeled; bound to a substrate, as in a microarray, such probes are typically, but not  
10       invariably unlabeled.

      In one embodiment, the isolated nucleic acid molecules of the present invention can be used as probes to detect and characterize gross alterations in the gene of a HSNA, such as deletions, insertions, translocations, and duplications of the HSNA genomic locus through fluorescence *in situ* hybridization (FISH) to chromosome spreads. *See, e.g.*,  
15       Andreeff *et al.* (eds.), Introduction to Fluorescence *In Situ* Hybridization: Principles and Clinical Applications, John Wiley & Sons (1999). The isolated nucleic acid molecules of the present invention can be used as probes to assess smaller genomic alterations using, *e.g.*, Southern blot detection of restriction fragment length polymorphisms. The isolated nucleic acid molecules of the present invention can be used as probes to isolate genomic  
20       clones that include a nucleic acid molecule of the present invention, which thereafter can be restriction mapped and sequenced to identify deletions, insertions, translocations, and substitutions (single nucleotide polymorphisms, SNPs) at the sequence level. Alternatively, detection techniques such as molecular beacons may be used, see Kostrikis *et al. Science* 279:1228-1229 (1998).

25       The isolated nucleic acid molecules of the present invention can be also be used as probes to detect, characterize, and quantify HSNA in, and isolate HSNA from, transcript-derived nucleic acid samples. In one embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by length, and quantify mRNA by Northern blot of total or poly-A<sup>+</sup>- selected RNA samples. In  
30       another embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by location, and quantify mRNA by *in situ* hybridization to tissue sections. *See, e.g.*, Schwarchzacher *et al.*, In Situ Hybridization, Springer-Verlag New York (2000). In another preferred embodiment, the

isolated nucleic acid molecules of the present invention can be used as hybridization probes to measure the representation of clones in a cDNA library or to isolate hybridizing nucleic acid molecules acids from cDNA libraries, permitting sequence level characterization of mRNAs that hybridize to HSNA, including, without limitations, identification of deletions, insertions, substitutions, truncations, alternatively spliced forms and single nucleotide polymorphisms. In yet another preferred embodiment, the nucleic acid molecules of the instant invention may be used in microarrays.

All of the aforementioned probe techniques are well within the skill in the art, and are described at greater length in standard texts such as Sambrook (2001), *supra*; Ausubel (1999), *supra*; and Walker *et al.* (eds.), The Nucleic Acids Protocols Handbook, Humana Press (2000).

In another embodiment, a nucleic acid molecule of the invention may be used as a probe or primer to identify and/or amplify a second nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of the invention. In this embodiment, it is preferred that the probe or primer be derived from a nucleic acid molecule encoding a HSP. More preferably, the probe or primer is derived from a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 410-611. Also preferred are probes or primers derived from a HSNA. More preferred are probes or primers derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-409.

In general, a probe or primer is at least 10 nucleotides in length, more preferably at least 12, more preferably at least 14 and even more preferably at least 16 or 17 nucleotides in length. In an even more preferred embodiment, the probe or primer is at least 18 nucleotides in length, even more preferably at least 20 nucleotides and even more preferably at least 22 nucleotides in length. Primers and probes may also be longer in length. For instance, a probe or primer may be 25 nucleotides in length, or may be 30, 40 or 50 nucleotides in length. Methods of performing nucleic acid hybridization using oligonucleotide probes are well known in the art. *See, e.g.*, Sambrook *et al.*, 1989, *supra*, Chapter 11 and pp. 11.31-11.32 and 11.40-11.44, which describes radiolabeling of short probes, and pp. 11.45-11.53, which describe hybridization conditions for oligonucleotide probes, including specific conditions for probe hybridization (pp. 11.50-11.51).

Methods of performing primer-directed amplification are also well known in the art. Methods for performing the polymerase chain reaction (PCR) are compiled, *inter alia*,

in McPherson, PCR Basics: From Background to Bench, Springer Verlag (2000); Innis *et al.* (eds.), PCR Applications: Protocols for Functional Genomics, Academic Press (1999); Gelfand *et al.* (eds.), PCR Strategies, Academic Press (1998); Newton *et al.*, PCR, Springer-Verlag New York (1997); Burke (ed.), PCR: Essential Techniques, John Wiley & Son Ltd (1996); White (ed.), PCR Cloning Protocols: From Molecular Cloning to Genetic Engineering, Vol. 67, Humana Press (1996); and McPherson *et al.* (eds.), PCR 2: A Practical Approach, Oxford University Press, Inc. (1995). Methods for performing RT-PCR are collected, *e.g.*, in Siebert *et al.* (eds.), Gene Cloning and Analysis by RT-PCR, Eaton Publishing Company/Bio Techniques Books Division, 1998; and Siebert (ed.), PCR Technique: RT-PCR, Eaton Publishing Company/ BioTechniques Books (1995).

PCR and hybridization methods may be used to identify and/or isolate nucleic acid molecules of the present invention including allelic variants, homologous nucleic acid molecules and fragments. PCR and hybridization methods may also be used to identify, amplify and/or isolate nucleic acid molecules of the present invention that encode homologous proteins, analogs, fusion protein or muteins of the invention. Nucleic acid primers as described herein can be used to prime amplification of nucleic acid molecules of the invention, using transcript-derived or genomic DNA as template.

These nucleic acid primers can also be used, for example, to prime single base extension (SBE) for SNP detection (*See, e.g.*, U.S. Pat. No. 6,004,744, the disclosure of which is incorporated herein by reference in its entirety).

Isothermal amplification approaches, such as rolling circle amplification, are also now well-described. *See, e.g.*, Schweitzer *et al.*, *Curr. Opin. Biotechnol.* 12(1): 21-7 (2001); international patent publications WO 97/19193 and WO 00/15779, and U.S. Patent Nos. 5,854,033 and 5,714,320, the disclosures of which are incorporated herein by reference in their entireties. Rolling circle amplification can be combined with other techniques to facilitate SNP detection. *See, e.g.*, Lizardi *et al.*, *Nature Genet.* 19(3): 225-32 (1998).

Nucleic acid molecules of the present invention may be bound to a substrate either covalently or noncovalently. The substrate can be porous or solid, planar or non-planar, unitary or distributed. The bound nucleic acid molecules may be used as hybridization probes, and may be labeled or unlabeled. In a preferred embodiment, the bound nucleic acid molecules are unlabeled.

In one embodiment, the nucleic acid molecule of the present invention is bound to a porous substrate, *e.g.*, a membrane, typically comprising nitrocellulose, nylon, or positively charged derivatized nylon. The nucleic acid molecule of the present invention can be used to detect a hybridizing nucleic acid molecule that is present within a labeled  
5 nucleic acid sample, *e.g.*, a sample of transcript-derived nucleic acids. In another embodiment, the nucleic acid molecule is bound to a solid substrate, including, without limitation, glass, amorphous silicon, crystalline silicon or plastics. Examples of plastics include, without limitation, polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene,  
10 polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof. The solid substrate may be any shape, including rectangular, disk-like and spherical. In a preferred embodiment, the solid substrate is a microscope slide or slide-shaped substrate.

The nucleic acid molecule of the present invention can be attached covalently to a  
15 surface of the support substrate or applied to a derivatized surface in a chaotropic agent that facilitates denaturation and adherence by presumed noncovalent interactions, or some combination thereof. The nucleic acid molecule of the present invention can be bound to a substrate to which a plurality of other nucleic acids are concurrently bound, hybridization to each of the plurality of bound nucleic acids being separately detectable. At low density,  
20 *e.g.* on a porous membrane, these substrate-bound collections are typically denominated macroarrays; at higher density, typically on a solid support, such as glass, these substrate bound collections of plural nucleic acids are colloquially termed microarrays. As used herein, the term microarray includes arrays of all densities. It is, therefore, another aspect of the invention to provide microarrays that comprise one or more of the nucleic acid  
25 molecules of the present invention.

In yet another embodiment, the invention is directed to single exon probes based on the HSNAs disclosed herein.

### *Expression Vectors, Host Cells and Recombinant Methods of Producing 30 Polypeptides*

Another aspect of the present invention provides vectors that comprise one or more of the isolated nucleic acid molecules of the present invention, and host cells in which such vectors have been introduced.

The vectors can be used, *inter alia*, for propagating the nucleic acid molecules of the present invention in host cells (cloning vectors), for shuttling the nucleic acid molecules of the present invention between host cells derived from disparate organisms (shuttle vectors), for inserting the nucleic acid molecules of the present invention into host cell chromosomes (insertion vectors), for expressing sense or antisense RNA transcripts of the nucleic acid molecules of the present invention *in vitro* or within a host cell, and for expressing polypeptides encoded by the nucleic acid molecules of the present invention, alone or as fusion proteins with heterologous polypeptides (expression vectors). Vectors are by now well known in the art, and are described, *inter alia*, in Jones *et al.* (eds.), Vectors: Cloning Applications: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Jones *et al.* (eds.), Vectors: Expression Systems: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Gacesa *et al.*, Vectors: Essential Data, John Wiley & Sons Ltd. (1995); Cid-Arregui (eds.), Viral Vectors: Basic Science and Gene Therapy, Eaton Publishing Co. (2000); Sambrook (2001), *supra*; Ausubel (1999), *supra*. Furthermore, a variety of vectors are available commercially. Use of existing vectors and modifications thereof are well within the skill in the art. Thus, only basic features need be described here.

Nucleic acid sequences may be expressed by operatively linking them to an expression control sequence in an appropriate expression vector and employing that expression vector to transform an appropriate unicellular host. Expression control sequences are sequences that control the transcription, post-transcriptional events and translation of nucleic acid sequences. Such operative linking of a nucleic sequence of this invention to an expression control sequence, of course, includes, if not already part of the nucleic acid sequence, the provision of a translation initiation codon, ATG or GTG, in the correct reading frame upstream of the nucleic acid sequence.

A wide variety of host/expression vector combinations may be employed in expressing the nucleic acid sequences of this invention. Useful expression vectors, for example, may consist of segments of chromosomal, non-chromosomal and synthetic nucleic acid sequences.

In one embodiment, prokaryotic cells may be used with an appropriate vector. Prokaryotic host cells are often used for cloning and expression. In a preferred embodiment, prokaryotic host cells include *E. coli*, *Pseudomonas*, *Bacillus* and *Streptomyces*. In a preferred embodiment, bacterial host cells are used to express the

nucleic acid molecules of the instant invention. Useful expression vectors for bacterial hosts include bacterial plasmids, such as those from *E. coli*, *Bacillus* or *Streptomyces*, including pBluescript, pGEX-2T, pUC vectors, col E1, pCR1, pBR322, pMB9 and their derivatives, wider host range plasmids, such as RP4, phage DNAs, *e.g.*, the numerous  
5 derivatives of phage lambda, *e.g.*, NM989,  $\lambda$ GT10 and  $\lambda$ GT11, and other phages, *e.g.*, M13 and filamentous single stranded phage DNA. Where *E. coli* is used as host, selectable markers are, analogously, chosen for selectivity in gram negative bacteria: *e.g.*, typical markers confer resistance to antibiotics, such as ampicillin, tetracycline, chloramphenicol, kanamycin, streptomycin and zeocin; auxotrophic markers can also be  
10 used.

In other embodiments, eukaryotic host cells, such as yeast, insect, mammalian or plant cells, may be used. Yeast cells, typically *S. cerevisiae*, are useful for eukaryotic genetic studies, due to the ease of targeting genetic changes by homologous recombination and the ability to easily complement genetic defects using recombinantly expressed  
15 proteins. Yeast cells are useful for identifying interacting protein components, *e.g.* through use of a two-hybrid system. In a preferred embodiment, yeast cells are useful for protein expression. Vectors of the present invention for use in yeast will typically, but not invariably, contain an origin of replication suitable for use in yeast and a selectable marker that is functional in yeast. Yeast vectors include Yeast Integrating plasmids (*e.g.*, YIp5)  
20 and Yeast Replicating plasmids (the YRp and YEplac series plasmids), Yeast Centromere plasmids (the YCp series plasmids), Yeast Artificial Chromosomes (YACs) which are based on yeast linear plasmids, denoted YLp, pGPD-2, 2 $\mu$  plasmids and derivatives thereof, and improved shuttle vectors such as those described in Gietz *et al.*, *Gene*, 74: 527-34 (1988) (YIplac, YEplac and YCplac). Selectable markers in yeast vectors include  
25 a variety of auxotrophic markers, the most common of which are (in *Saccharomyces cerevisiae*) URA3, HIS3, LEU2, TRP1 and LYS2, which complement specific auxotrophic mutations, such as *ura3-52*, *his3-D1*, *leu2-D1*, *trp1-D1* and *lys2-201*.

Insect cells may be chosen for high efficiency protein expression. Where the host cells are from *Spodoptera frugiperda*, *e.g.*, Sf9 and Sf21 cell lines, and expresSF™ cells  
30 (Protein Sciences Corp., Meriden, CT, USA), the vector replicative strategy is typically based upon the baculovirus life cycle. Typically, baculovirus transfer vectors are used to replace the wild-type AcMNPV polyhedrin gene with a heterologous gene of interest. Sequences that flank the polyhedrin gene in the wild-type genome are positioned 5' and 3'

of the expression cassette on the transfer vectors. Following co-transfection with AcMNPV DNA, a homologous recombination event occurs between these sequences resulting in a recombinant virus carrying the gene of interest and the polyhedrin or p10 promoter. Selection can be based upon visual screening for lacZ fusion activity.

5           The host cells may also be mammalian cells, which are particularly useful for expression of proteins intended as pharmaceutical agents, and for screening of potential agonists and antagonists of a protein or a physiological pathway. Mammalian vectors intended for autonomous extrachromosomal replication will typically include a viral origin, such as the SV40 origin (for replication in cell lines expressing the large T-antigen, 10 such as COS1 and COS7 cells), the papillomavirus origin, or the EBV origin for long term episomal replication (for use, *e.g.*, in 293-EBNA cells, which constitutively express the EBV EBNA-1 gene product and adenovirus E1A). Vectors intended for integration, and thus replication as part of the mammalian chromosome, can, but need not, include an origin of replication functional in mammalian cells, such as the SV40 origin. Vectors 15 based upon viruses, such as adenovirus, adeno-associated virus, vaccinia virus, and various mammalian retroviruses, will typically replicate according to the viral replicative strategy. Selectable markers for use in mammalian cells include, include but are not limited to, resistance to neomycin (G418), blasticidin, hygromycin and zeocin, and selection based upon the purine salvage pathway using HAT medium.

20           Expression in mammalian cells can be achieved using a variety of plasmids, including pSV2, pBC12BI, and p91023, as well as lytic virus vectors (*e.g.*, vaccinia virus, adeno virus, and baculovirus), episomal virus vectors (*e.g.*, bovine papillomavirus), and retroviral vectors (*e.g.*, murine retroviruses). Useful vectors for insect cells include baculoviral vectors and pVL 941.

25           Plant cells can also be used for expression, with the vector replicon typically derived from a plant virus (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) and selectable markers chosen for suitability in plants.

          It is known that codon usage of different host cells may be different. For example, a plant cell and a human cell may exhibit a difference in codon preference for encoding a 30 particular amino acid. As a result, human mRNA may not be efficiently translated in a plant, bacteria or insect host cell. Therefore, another embodiment of this invention is directed to codon optimization. The codons of the nucleic acid molecules of the invention

may be modified to resemble, as much as possible, genes naturally contained within the host cell without altering the amino acid sequence encoded by the nucleic acid molecule.

Any of a wide variety of expression control sequences may be used in these vectors to express the nucleic acid molecules of this invention. Such useful expression control sequences include the expression control sequences associated with structural genes of the foregoing expression vectors. Expression control sequences that control transcription include, *e.g.*, promoters, enhancers and transcription termination sites. Expression control sequences in eukaryotic cells that control post-transcriptional events include splice donor and acceptor sites and sequences that modify the half-life of the transcribed RNA, *e.g.*, sequences that direct poly(A) addition or binding sites for RNA-binding proteins. Expression control sequences that control translation include ribosome binding sites, sequences which direct targeted expression of the polypeptide to or within particular cellular compartments, and sequences in the 5' and 3' untranslated regions that modify the rate or efficiency of translation.

Examples of useful expression control sequences for a prokaryote, *e.g.*, *E. coli*, will include a promoter, often a phage promoter, such as phage lambda pL promoter, the *trc* promoter, a hybrid derived from the *trp* and *lac* promoters, the bacteriophage T7 promoter (in *E. coli* cells engineered to express the T7 polymerase), the TAC or TRC system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, and the *araBAD* operon. Prokaryotic expression vectors may further include transcription terminators, such as the *aspA* terminator, and elements that facilitate translation, such as a consensus ribosome binding site and translation termination codon, Schomer *et al.*, *Proc. Natl. Acad. Sci. USA* 83: 8506-8510 (1986).

Expression control sequences for yeast cells, typically *S. cerevisiae*, will include a yeast promoter, such as the CYC1 promoter, the GAL1 promoter, the GAL10 promoter, ADH1 promoter, the promoters of the yeast  $\alpha$ -mating system, or the GPD promoter, and will typically have elements that facilitate transcription termination, such as the transcription termination signals from the CYC1 or ADH1 gene.

Expression vectors useful for expressing proteins in mammalian cells will include a promoter active in mammalian cells. These promoters include, but are not limited to, those derived from mammalian viruses, such as the enhancer-promoter sequences from the immediate early gene of the human cytomegalovirus (CMV), the enhancer-promoter sequences from the Rous sarcoma virus long terminal repeat (RSV LTR), the enhancer-



promoter from SV40 and the early and late promoters of adenovirus. Other expression control sequences include the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase. Other expression control sequences include those from the gene comprising the HSNA of interest. Often, expression is enhanced by  
5 incorporation of polyadenylation sites, such as the late SV40 polyadenylation site and the polyadenylation signal and transcription termination sequences from the bovine growth hormone (BGH) gene, and ribosome binding sites. Furthermore, vectors can include introns, such as intron II of rabbit  $\beta$ -globin gene and the SV40 splice elements.

Preferred nucleic acid vectors also include a selectable or amplifiable marker gene  
10 and means for amplifying the copy number of the gene of interest. Such marker genes are well known in the art. Nucleic acid vectors may also comprise stabilizing sequences (*e.g.*, ori- or ARS-like sequences and telomere-like sequences), or may alternatively be designed to favor directed or non-directed integration into the host cell genome. In a preferred embodiment, nucleic acid sequences of this invention are inserted in frame into an  
15 expression vector that allows a high level expression of an RNA which encodes a protein comprising the encoded nucleic acid sequence of interest. Nucleic acid cloning and sequencing methods are well known to those of skill in the art and are described in an assortment of laboratory manuals, including Sambrook (1989), *supra*, Sambrook (2000), *supra*; and Ausubel (1992), *supra*, Ausubel (1999), *supra*. Product information from  
20 manufacturers of biological, chemical and immunological reagents also provide useful information.

Expression vectors may be either constitutive or inducible. Inducible vectors include either naturally inducible promoters, such as the *trc* promoter, which is regulated by the *lac* operon, and the *pL* promoter, which is regulated by tryptophan, the  
25 MMTV-LTR promoter, which is inducible by dexamethasone, or can contain synthetic promoters and/or additional elements that confer inducible control on adjacent promoters. Examples of inducible synthetic promoters are the hybrid *Plac/ara-1* promoter and the *PLtetO-1* promoter. The *PLtetO-1* promoter takes advantage of the high expression levels from the *PL* promoter of phage lambda, but replaces the lambda repressor sites with two  
30 copies of operator 2 of the *Tn10* tetracycline resistance operon, causing this promoter to be tightly repressed by the Tet repressor protein and induced in response to tetracycline (Tc) and Tc derivatives such as anhydrotetracycline. Vectors may also be inducible because they contain hormone response elements, such as the glucocorticoid response

element (GRE) and the estrogen response element (ERE), which can confer hormone inducibility where vectors are used for expression in cells having the respective hormone receptors. To reduce background levels of expression, elements responsive to ecdysone, an insect hormone, can be used instead, with coexpression of the ecdysone receptor.

5 In one embodiment of the invention, expression vectors can be designed to fuse the expressed polypeptide to small protein tags that facilitate purification and/or visualization. Such tags include a polyhistidine tag that facilitates purification of the fusion protein by immobilized metal affinity chromatography, for example using NiNTA resin (Qiagen Inc., Valencia, CA, USA) or TALON™ resin (cobalt immobilized affinity chromatography  
10 medium, Clontech Labs, Palo Alto, CA, USA). The fusion protein can include a chitin-binding tag and self-excising intein, permitting chitin-based purification with self-removal of the fused tag (IMPACT™ system, New England Biolabs, Inc., Beverly, MA, USA). Alternatively, the fusion protein can include a calmodulin-binding peptide tag, permitting purification by calmodulin affinity resin (Stratagene, La Jolla, CA, USA), or a specifically  
15 excisable fragment of the biotin carboxylase carrier protein, permitting purification of *in vivo* biotinylated protein using an avidin resin and subsequent tag removal (Promega, Madison, WI, USA). As another useful alternative, the polypeptides of the present invention can be expressed as a fusion to glutathione-S-transferase, the affinity and specificity of binding to glutathione permitting purification using glutathione affinity  
20 resins, such as Glutathione-Superflow Resin (Clontech Laboratories, Palo Alto, CA, USA), with subsequent elution with free glutathione. Other tags include, for example, the Xpress epitope, detectable by anti-Xpress antibody (Invitrogen, Carlsbad, CA, USA), a myc tag, detectable by anti-myc tag antibody, the V5 epitope, detectable by anti-V5 antibody (Invitrogen, Carlsbad, CA, USA), FLAG® epitope, detectable by anti-FLAG®  
25 antibody (Stratagene, La Jolla, CA, USA), and the HA epitope, detectable by anti-HA antibody.

For secretion of expressed polypeptides, vectors can include appropriate sequences that encode secretion signals, such as leader peptides. For example, the pSecTag2 vectors (Invitrogen, Carlsbad, CA, USA) are 5.2 kb mammalian expression vectors that carry the  
30 secretion signal from the V-J2-C region of the mouse Ig kappa-chain for efficient secretion of recombinant proteins from a variety of mammalian cell lines.

Expression vectors can also be designed to fuse proteins encoded by the heterologous nucleic acid insert to polypeptides that are larger than purification and/or

identification tags. Useful protein fusions include those that permit display of the encoded protein on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, such as those that have a green fluorescent protein (GFP)-like chromophore, fusions to the IgG Fc region, and fusions for use in two hybrid systems.

- 5            Vectors for phage display fuse the encoded polypeptide to, *e.g.*, the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13. *See* Barbas *et al.*, Phage Display: A Laboratory Manual, Cold Spring Harbor Laboratory Press (2001); Kay *et al.* (eds.), Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press, Inc., (1996); Abelson *et al.* (eds.), Combinatorial  
10 Chemistry (Methods in Enzymology, Vol. 267) Academic Press (1996). Vectors for yeast display, *e.g.* the pYD1 yeast display vector (Invitrogen, Carlsbad, CA, USA), use the  $\alpha$ -agglutinin yeast adhesion receptor to display recombinant protein on the surface of *S. cerevisiae*. Vectors for mammalian display, *e.g.*, the pDisplay™ vector (Invitrogen, Carlsbad, CA, USA), target recombinant proteins using an N-terminal cell surface  
15 targeting signal and a C-terminal transmembrane anchoring domain of platelet derived growth factor receptor.

- A wide variety of vectors now exist that fuse proteins encoded by heterologous nucleic acids to the chromophore of the substrate-independent, intrinsically fluorescent green fluorescent protein from *Aequorea victoria* ("GFP") and its variants. The GFP-like  
20 chromophore can be selected from GFP-like chromophores found in naturally occurring proteins, such as *A. victoria* GFP (GenBank accession number AAA27721), *Renilla reniformis* GFP, FP583 (GenBank accession no. AF168419) (DsRed), FP593 (AF272711), FP483 (AF168420), FP484 (AF168424), FP595 (AF246709), FP486 (AF168421), FP538 (AF168423), and FP506 (AF168422), and need include only so much of the native protein  
25 as is needed to retain the chromophore's intrinsic fluorescence. Methods for determining the minimal domain required for fluorescence are known in the art. *See* Li *et al.*, *J. Biol. Chem.* 272: 28545-28549 (1997). Alternatively, the GFP-like chromophore can be selected from GFP-like chromophores modified from those found in nature. The methods for engineering such modified GFP-like chromophores and testing them for fluorescence  
30 activity, both alone and as part of protein fusions, are well known in the art. *See* Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Palm *et al.*, *Methods Enzymol.* 302: 378-394 (1999). A variety of such modified chromophores are now commercially available and can readily be used in the fusion proteins of the present invention. These include EGFP ("enhanced

GFP”), EBFP (“enhanced blue fluorescent protein”), BFP2, EYFP (“enhanced yellow fluorescent protein”), ECFP (“enhanced cyan fluorescent protein”) or Citrine. EGFP (*see, e.g., Cormack et al., Gene* 173: 33–38 (1996); U.S. Patent Nos. 6,090,919 and 5,804,387, the disclosures of which are incorporated herein by reference in their entireties) is found  
5 on a variety of vectors, both plasmid and viral, which are available commercially (Clontech Labs, Palo Alto, CA, USA); EBFP is optimized for expression in mammalian cells whereas BFP2, which retains the original jellyfish codons, can be expressed in bacteria (*see, e.g., Heim et al., Curr. Biol.* 6: 178–182 (1996) and Cormack et al., *Gene* 173: 33–38 (1996)). Vectors containing these blue-shifted variants are available from  
10 Clontech Labs (Palo Alto, CA, USA). Vectors containing EYFP, ECFP (*see, e.g., Heim et al., Curr. Biol.* 6: 178–182 (1996); Miyawaki et al., *Nature* 388: 882–887 (1997)) and Citrine (*see, e.g., Heikal et al., Proc. Natl. Acad. Sci. USA* 97: 11996–12001 (2000)) are also available from Clontech Labs. The GFP-like chromophore can also be drawn from other modified GFPs, including those described in U.S. Patent Nos. 6,124,128; 6,096,865;  
15 6,090,919; 6,066,476; 6,054,321; 6,027,881; 5,968,750; 5,874,304; 5,804,387; 5,777,079; 5,741,668; and 5,625,048, the disclosures of which are incorporated herein by reference in their entireties. *See also Conn (ed.), Green Fluorescent Protein* (Methods in Enzymology, Vol. 302), Academic Press, Inc. (1999); Yang, et al., *J Biol Chem*, 273: 8212–6 (1998); Bevis et al., *Nature Biotechnology*, 20:83–7 (2002). The GFP-like chromophore of each  
20 of these GFP variants can usefully be included in the fusion proteins of the present invention.

Fusions to the IgG Fc region increase serum half-life of protein pharmaceutical products through interaction with the FcRn receptor (also denominated the FcRp receptor and the Brambell receptor, FcRb), further described in International Patent Application  
25 nos. WO 97/43316, WO 97/34631, WO 96/32478, WO 96/18412, the disclosures of which are incorporated herein by reference in their entireties.

For long-term, high-yield recombinant production of the polypeptides of the present invention, stable expression is preferred. Stable expression is readily achieved by integration into the host cell genome of vectors having selectable markers, followed by  
30 selection of these integrants. Vectors such as pUB6/V5-His A, B, and C (Invitrogen, Carlsbad, CA, USA) are designed for high-level stable expression of heterologous proteins in a wide range of mammalian tissue types and cell lines. pUB6/V5-His uses the promoter/enhancer sequence from the human ubiquitin C gene to drive expression of

recombinant proteins: expression levels in 293, CHO, and NIH3T3 cells are comparable to levels from the CMV and human EF-1a promoters. The *bsd* gene permits rapid selection of stably transfected mammalian cells with the potent antibiotic blasticidin.

Replication incompetent retroviral vectors, typically derived from Moloney murine leukemia virus, also are useful for creating stable transfectants having integrated provirus. The highly efficient transduction machinery of retroviruses, coupled with the availability of a variety of packaging cell lines such as RetroPack™ PT 67, EcoPack2™-293, AmphoPack-293, and GP2-293 cell lines (all available from Clontech Laboratories, Palo Alto, CA, USA) allow a wide host range to be infected with high efficiency; varying the multiplicity of infection readily adjusts the copy number of the integrated provirus.

Of course, not all vectors and expression control sequences will function equally well to express the nucleic acid molecules of this invention. Neither will all hosts function equally well with the same expression system. However, one of skill in the art may make a selection among these vectors, expression control sequences and hosts without undue experimentation and without departing from the scope of this invention. For example, in selecting a vector, the host must be considered because the vector must be replicated in it. The vector's copy number, the ability to control that copy number, the ability to control integration, if any, and the expression of any other proteins encoded by the vector, such as antibiotic or other selection markers, should also be considered. The present invention further includes host cells comprising the vectors of the present invention, either present episomally within the cell or integrated, in whole or in part, into the host cell chromosome. Among other considerations, some of which are described above, a host cell strain may be chosen for its ability to process the expressed polypeptide in the desired fashion. Such post-translational modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation, and it is an aspect of the present invention to provide HSPs with such post-translational modifications.

In selecting an expression control sequence, a variety of factors should also be considered. These include, for example, the relative strength of the sequence, its controllability, and its compatibility with the nucleic acid molecules of this invention, particularly with regard to potential secondary structures. Unicellular hosts should be selected by consideration of their compatibility with the chosen vector, the toxicity of the product coded for by the nucleic acid sequences of this invention, their secretion

characteristics, their ability to fold the polypeptide correctly, their fermentation or culture requirements, and the ease of purification from them of the products coded for by the nucleic acid molecules of this invention.

5 The recombinant nucleic acid molecules and more particularly, the expression vectors of this invention may be used to express the polypeptides of this invention as recombinant polypeptides in a heterologous host cell. The polypeptides of this invention may be full-length or less than full-length polypeptide fragments recombinantly expressed from the nucleic acid molecules according to this invention. Such polypeptides include analogs, derivatives and muteins that may or may not have biological activity.

10 Vectors of the present invention will also often include elements that permit *in vitro* transcription of RNA from the inserted heterologous nucleic acid. Such vectors typically include a phage promoter, such as that from T7, T3, or SP6, flanking the nucleic acid insert. Often two different such promoters flank the inserted nucleic acid, permitting separate *in vitro* production of both sense and antisense strands.

15 Transformation and other methods of introducing nucleic acids into a host cell (*e.g.*, conjugation, protoplast transformation or fusion, transfection, electroporation, liposome delivery, membrane fusion techniques, high velocity DNA-coated pellets, viral infection and protoplast fusion) can be accomplished by a variety of methods which are well known in the art (*See*, for instance, Ausubel, *supra*, and Sambrook *et al.*, *supra*).

20 Bacterial, yeast, plant or mammalian cells are transformed or transfected with an expression vector, such as a plasmid, a cosmid, or the like, wherein the expression vector comprises the nucleic acid of interest. Alternatively, the cells may be infected by a viral expression vector comprising the nucleic acid of interest. Depending upon the host cell, vector, and method of transformation used, transient or stable expression of the  
25 polypeptide will be constitutive or inducible. One having ordinary skill in the art will be able to decide whether to express a polypeptide transiently or stably, and whether to express the protein constitutively or inducibly.

A wide variety of unicellular host cells are useful in expressing the DNA sequences of this invention. These hosts may include well known eukaryotic and  
30 prokaryotic hosts, such as strains of, fungi, yeast, insect cells such as *Spodoptera frugiperda* (SF9), animal cells such as CHO, as well as plant cells in tissue culture. Representative examples of appropriate host cells include, but are not limited to, bacterial cells, such as *E. coli*, *Caulobacter crescentus*, *Streptomyces* species, and *Salmonella*

*typhimurium*; yeast cells, such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Pichia pastoris*, *Pichia methanolica*; insect cell lines, such as those from *Spodoptera frugiperda* — e.g., Sf9 and Sf21 cell lines, and expresSFTM cells (Protein Sciences Corp.; Meriden, CT, USA) — *Drosophila* S2 cells, and *Trichoplusia ni* High Five® Cells

5 (Invitrogen, Carlsbad, CA, USA); and mammalian cells. Typical mammalian cells include BHK cells, BSC 1 cells, BSC 40 cells, BMT 10 cells, VERO cells, COS1 cells, COS7 cells, Chinese hamster ovary (CHO) cells, 3T3 cells, NIH 3T3 cells, 293 cells, HEPG2 cells, HeLa cells, L cells, MDCK cells, HEK293 cells, WI38 cells, murine ES cell lines (e.g., from strains 129/SV, C57/BL6, DBA-1, 129/SVJ), K562 cells, Jurkat cells, and

10 BW5147 cells. Other mammalian cell lines are well known and readily available from the American Type Culture Collection (ATCC) (Manassas, VA, USA) and the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the Coriell Cell Repositories (Camden, NJ, USA). Cells or cell lines derived from hepatic are particularly preferred because they may provide a more native post-translational

15 processing. Particularly preferred are human hepatic cells.

Particular details of the transfection, expression and purification of recombinant proteins are well documented and are understood by those of skill in the art. Further details on the various technical aspects of each of the steps used in recombinant production of foreign genes in bacterial cell expression systems can be found in a number

20 of texts and laboratory manuals in the art. See, e.g., Ausubel (1992), *supra*, Ausubel (1999), *supra*, Sambrook (1989), *supra*, and Sambrook (2001), *supra*.

Methods for introducing the vectors and nucleic acid molecules of the present invention into the host cells are well known in the art; the choice of technique will depend primarily upon the specific vector to be introduced and the host cell chosen.

25 Nucleic acid molecules and vectors may be introduced into prokaryotes, such as *E. coli*, in a number of ways. For instance, phage lambda vectors will typically be packaged using a packaging extract (e.g., Gigapack® packaging extract, Stratagene, La Jolla, CA, USA), and the packaged virus used to infect *E. coli*.

Plasmid vectors will typically be introduced into chemically competent or

30 electrocompetent bacterial cells. *E. coli* cells can be rendered chemically competent by treatment, e.g., with CaCl<sub>2</sub>, or a solution of Mg<sup>2+</sup>, Mn<sup>2+</sup>, Ca<sup>2+</sup>, Rb<sup>+</sup> or K<sup>+</sup>, dimethyl sulfoxide, dithiothreitol, and hexamine cobalt (III), Hanahan, *J. Mol. Biol.* 166(4):557-80 (1983), and vectors introduced by heat shock. A wide variety of chemically competent

strains are also available commercially (e.g., Epicurian Coli® XL10-Gold® Ultracompetent Cells (Stratagene, La Jolla, CA, USA); DH5α competent cells (Clontech Laboratories, Palo Alto, CA, USA); and TOP10 Chemically Competent E. coli Kit (Invitrogen, Carlsbad, CA, USA)). Bacterial cells can be rendered electrocompetent to  
5 take up exogenous DNA by electroporation by various pre-pulse treatments; vectors are introduced by electroporation followed by subsequent outgrowth in selected media. An extensive series of protocols is provided by BioRad (Richmond, CA, USA).

Vectors can be introduced into yeast cells by spheroplasting, treatment with lithium salts, electroporation, or protoplast fusion. Spheroplasts are prepared by the action  
10 of hydrolytic enzymes such as a snail-gut extract, usually denoted Glusulase or Zymolyase, or an enzyme from *Arthrobacter luteus* to remove portions of the cell wall in the presence of osmotic stabilizers, typically 1 M sorbitol. DNA is added to the spheroplasts, and the mixture is co-precipitated with a solution of polyethylene glycol (PEG) and  $\text{Ca}^{2+}$ . Subsequently, the cells are resuspended in a solution of sorbitol, mixed  
15 with molten agar and then layered on the surface of a selective plate containing sorbitol.

For lithium-mediated transformation, yeast cells are treated with lithium acetate to permeabilize the cell wall, DNA is added and the cells are co-precipitated with PEG. The cells are exposed to a brief heat shock, washed free of PEG and lithium acetate, and subsequently spread on plates containing ordinary selective medium. Increased  
20 frequencies of transformation are obtained by using specially-prepared single-stranded carrier DNA and certain organic solvents. Schiestl *et al.*, *Curr. Genet.* 16(5-6): 339-46 (1989).

For electroporation, freshly-grown yeast cultures are typically washed, suspended in an osmotic protectant, such as sorbitol, mixed with DNA, and the cell suspension  
25 pulsed in an electroporation device. Subsequently, the cells are spread on the surface of plates containing selective media. Becker *et al.*, *Methods Enzymol.* 194: 182-187 (1991). The efficiency of transformation by electroporation can be increased over 100-fold by using PEG, single-stranded carrier DNA and cells that are in late log-phase of growth. Larger constructs, such as YACs, can be introduced by protoplast fusion.

30 Mammalian and insect cells can be directly infected by packaged viral vectors, or transfected by chemical or electrical means. For chemical transfection, DNA can be coprecipitated with  $\text{CaPO}_4$  or introduced using liposomal and nonliposomal lipid-based agents. Commercial kits are available for  $\text{CaPO}_4$  transfection (CalPhos™ Mammalian



Transfection Kit, Clontech Laboratories, Palo Alto, CA, USA), and lipid-mediated transfection can be practiced using commercial reagents, such as LIPOFECTAMINE™ 2000, LIPOFECTAMINE™ Reagent, CELLFECTIN® Reagent, and LIPOFECTIN® Reagent (Invitrogen, Carlsbad, CA, USA), DOTAP Liposomal Transfection Reagent, FuGENE 6, X-tremeGENE Q2, DOSPER, (Roche Molecular Biochemicals, Indianapolis, IN USA), Effectene™, PolyFect®, Superfect® (Qiagen, Inc., Valencia, CA, USA). Protocols for electroporating mammalian cells can be found in, for example, ; Norton *et al.* (eds.), Gene Transfer Methods: Introducing DNA into Living Cells and Organisms, BioTechniques Books, Eaton Publishing Co. (2000). Other transfection techniques include transfection by particle bombardment and microinjection. See, e.g., Cheng *et al.*, *Proc. Natl. Acad. Sci. USA* 90(10): 4455-9 (1993); Yang *et al.*, *Proc. Natl. Acad. Sci. USA* 87(24): 9568-72 (1990).

Production of the recombinantly produced proteins of the present invention can optionally be followed by purification.

Purification of recombinantly expressed proteins is now well within the skill in the art and thus need not be detailed here. See, e.g., Thorner *et al.* (eds.), Applications of Chimeric Genes and Hybrid Proteins, Part A: Gene Expression and Protein Purification (Methods in Enzymology, Vol. 326), Academic Press (2000); Harbin (ed.), Cloning, Gene Expression and Protein Purification : Experimental Procedures and Process Rationale, Oxford Univ. Press (2001); Marshak *et al.*, Strategies for Protein Purification and Characterization: A Laboratory Course Manual, Cold Spring Harbor Laboratory Press (1996); and Roe (ed.), Protein Purification Applications, Oxford University Press (2001).

Briefly, however, if purification tags have been fused through use of an expression vector that appends such tag, purification can be effected, at least in part, by means appropriate to the tag, such as use of immobilized metal affinity chromatography for polyhistidine tags. Other techniques common in the art include ammonium sulfate fractionation, immunoprecipitation, fast protein liquid chromatography (FPLC), high performance liquid chromatography (HPLC), and preparative gel electrophoresis.

Polypeptides, including Fragments Muteins, Homologous Proteins, Allelic Variants, Analogs and Derivatives

Another aspect of the invention relates to polypeptides encoded by the nucleic acid molecules described herein. In a preferred embodiment, the polypeptide is a hepatic

specific polypeptide (HSP). In an even more preferred embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO:410-611 or is derived from a polypeptide having the amino acid sequence of SEQ ID NO: 410-611. A polypeptide as defined herein may be produced recombinantly, as discussed *supra*, may be isolated from  
5 a cell that naturally expresses the protein, or may be chemically synthesized following the teachings of the specification and using methods well known to those having ordinary skill in the art.

Polypeptides of the present invention may also comprise a part or fragment of a HSP. In a preferred embodiment, the fragment is derived from a polypeptide having an  
10 amino acid sequence selected from the group consisting of SEQ ID NO: 410-611. Polypeptides of the present invention comprising a part or fragment of an entire HSP may or may not be HSPs. For example, a full-length polypeptide may be hepatic-specific, while a fragment thereof may be found in other tissues as well as in hepatic. A polypeptide that is not a HSP, whether it is a fragment, analog, mutein, homologous  
15 protein or derivative, is nevertheless useful, especially for immunizing animals to prepare anti-HSP antibodies. In a preferred embodiment, the part or fragment is a HSP. Methods of determining whether a polypeptide of the present invention is a HSP are described *infra*.

Polypeptides of the present invention comprising fragments of at least 6  
20 contiguous amino acids are also useful in mapping B cell and T cell epitopes of the reference protein. See, e.g., Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81: 3998-4002 (1984) and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. Because the fragment need not itself be immunogenic, part of an immunodominant epitope, nor even recognized by native  
25 antibody, to be useful in such epitope mapping, all fragments of at least 6 amino acids of a polypeptide of the present invention have utility in such a study.

Polypeptides of the present invention comprising fragments of at least 8 contiguous amino acids, often at least 15 contiguous amino acids, are useful as immunogens for raising antibodies that recognize polypeptides of the present invention.  
30 See, e.g., Lerner, *Nature* 299: 592-596 (1982); Shinnick *et al.*, *Annu. Rev. Microbiol.* 37: 425-46 (1983); Sutcliffe *et al.*, *Science* 219: 660-6 (1983). As further described in the above-cited references, virtually all 8-mers, conjugated to a carrier, such as a protein, prove immunogenic and are capable of eliciting antibody for the conjugated peptide;

accordingly, all fragments of at least 8 amino acids of the polypeptides of the present invention have utility as immunogens.

Polypeptides comprising fragments of at least 8, 9, 10 or 12 contiguous amino acids are also useful as competitive inhibitors of binding of the entire polypeptide, or a portion thereof, to antibodies (as in epitope mapping), and to natural binding partners, such as subunits in a multimeric complex or to receptors or ligands of the subject protein; this competitive inhibition permits identification and separation of molecules that bind specifically to the polypeptide of interest. See U.S. Patent Nos. 5,539,084 and 5,783,674, incorporated herein by reference in their entireties.

The polypeptide of the present invention thus preferably is at least 6 amino acids in length, typically at least 8, 9, 10 or 12 amino acids in length, and often at least 15 amino acids in length. Often, the polypeptide of the present invention is at least 20 amino acids in length, even 25 amino acids, 30 amino acids, 35 amino acids, or 50 amino acids or more in length. Of course, larger polypeptides having at least 75 amino acids, 100 amino acids, or even 150 amino acids are also useful, and at times preferred.

One having ordinary skill in the art can produce fragments by truncating the nucleic acid molecule, *e.g.*, a HSNA, encoding the polypeptide and then expressing it recombinantly. Alternatively, one can produce a fragment by chemically synthesizing a portion of the full-length polypeptide. One may also produce a fragment by enzymatically cleaving either a recombinant polypeptide or an isolated naturally occurring polypeptide. Methods of producing polypeptide fragments are well known in the art. *See, e.g.*, Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. In one embodiment, a polypeptide comprising only a fragment, preferably a fragment of a HSP, may be produced by chemical or enzymatic cleavage of a HSP polypeptide. In a preferred embodiment, a polypeptide fragment is produced by expressing a nucleic acid molecule of the present invention encoding a fragment, preferably of a HSP, in a host cell.

Polypeptides of the present invention are also inclusive of mutants, fusion proteins, homologous proteins and allelic variants.

A mutant protein, or mutein, may have the same or different properties compared to a naturally occurring polypeptide and comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of a native polypeptide. Small deletions and insertions can often be found that do not alter

the function of a protein. Muteins may or may not be hepatic-specific. Preferably, the mutein is hepatic-specific. More preferably the mutein is a polypeptide that comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of SEQ ID NO: 410-611. Accordingly, in a preferred embodiment, the mutein is one that exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a HSP comprising an amino acid sequence of SEQ ID NO: 410-611. In a yet more preferred embodiment, the mutein exhibits at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97%, 98%, 99% or 99.5% sequence identity to a HSP comprising an amino acid sequence of SEQ ID NO: 410-611.

A mutein may be produced by isolation from a naturally occurring mutant cell, tissue or organism. A mutein may be produced by isolation from a cell, tissue or organism that has been experimentally mutagenized. Alternatively, a mutein may be produced by chemical manipulation of a polypeptide, such as by altering the amino acid residue to another amino acid residue using synthetic or semi-synthetic chemical techniques. In a preferred embodiment, a mutein is produced from a host cell comprising a mutated nucleic acid molecule compared to the naturally occurring nucleic acid molecule. For instance, one may produce a mutein of a polypeptide by introducing one or more mutations into a nucleic acid molecule of the invention and then expressing it recombinantly. These mutations may be targeted, in which particular encoded amino acids are altered, or may be untargeted, in which random encoded amino acids within the polypeptide are altered. Muteins with random amino acid alterations can be screened for a particular biological activity or property, particularly whether the polypeptide is hepatic-specific, as described below. Multiple random mutations can be introduced into the gene by methods well known to the art, *e.g.*, by error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, *in vivo* mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis and site-specific mutagenesis. Methods of producing muteins with targeted or random amino acid alterations are well known in the art. *See, e.g.*, Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), as well as U.S. Patent No. 5,223,408, which is herein incorporated by reference in its entirety.

The invention also contemplates polypeptides that are homologous to a polypeptide of the invention. In a preferred embodiment, the polypeptide is homologous to a HSP. In an even more preferred embodiment, the polypeptide is homologous to a HSP selected from the group having an amino acid sequence of SEQ ID NO: 410-611. By  
5 homologous polypeptide it is means one that exhibits significant sequence identity to a HSP, preferably a HSP having an amino acid sequence of SEQ ID NO: 410-611. By significant sequence identity it is meant that the homologous polypeptide exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a HSP  
10 comprising an amino acid sequence of SEQ ID NO: 410-611. More preferred are homologous polypeptides exhibiting at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97% or 98% sequence identity to a HSP comprising an amino acid sequence of SEQ ID NO: 410-611. Most preferably, the homologous polypeptide exhibits at least 99%, more preferably 99.5%, even more  
15 preferably 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a HSP comprising an amino acid sequence of SEQ ID NO: 410-611. In a preferred embodiment, the amino acid substitutions of the homologous polypeptide are conservative amino acid substitutions as discussed above.

Homologous polypeptides of the present invention also comprise polypeptide  
20 encoded by a nucleic acid molecule that selectively hybridizes to a HSNA or an antisense sequence thereof. In this embodiment, it is preferred that the homologous polypeptide be encoded by a nucleic acid molecule that hybridizes to a HSNA under low stringency, moderate stringency or high stringency conditions, as defined herein. More preferred is a homologous polypeptide encoded by a nucleic acid sequence which hybridizes to a HSNA  
25 selected from the group consisting of SEQ ID NO: 1-409 or a homologous polypeptide encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule that encodes a HSP, preferably an HSP of SEQ ID NO: 410-611 under low stringency, moderate stringency or high stringency conditions, as defined herein.

Homologous polypeptides of the present invention may be naturally occurring and  
30 derived from another species, especially one derived from another primate, such as chimpanzee, gorilla, rhesus macaque, or baboon, wherein the homologous polypeptide comprises an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 410-611. The homologous polypeptide may also be a naturally occurring

polypeptide from a human, when the HSP is a member of a family of polypeptides. The homologous polypeptide may also be a naturally occurring polypeptide derived from a non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, guinea pig, hamster, cow, horse, goat or pig. The homologous polypeptide may also be a naturally occurring polypeptide derived from a non-mammalian species, such as birds or reptiles. The naturally occurring homologous protein may be isolated directly from humans or other species. Alternatively, the nucleic acid molecule encoding the naturally occurring homologous polypeptide may be isolated and used to express the homologous polypeptide recombinantly. The homologous polypeptide may also be one that is experimentally produced by random mutation of a nucleic acid molecule and subsequent expression of the nucleic acid molecule. Alternatively, the homologous polypeptide may be one that is experimentally produced by directed mutation of one or more codons to alter the encoded amino acid of a HSP. In a preferred embodiment, the homologous polypeptide encodes a polypeptide that is a HSP.

Relatedness of proteins can also be characterized using a second functional test, the ability of a first protein competitively to inhibit the binding of a second protein to an antibody. It is, therefore, another aspect of the present invention to provide isolated polypeptide not only identical in sequence to those described with particularity herein, but also to provide isolated polypeptide ("cross-reactive proteins") that competitively inhibit the binding of antibodies to all or to a portion of various of the isolated polypeptides of the present invention. Such competitive inhibition can readily be determined using immunoassays well known in the art.

As discussed above, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes, and the sequence determined from one individual of a species may differ from other allelic forms present within the population. Thus, polypeptides of the present invention are also inclusive of those encoded by an allelic variant of a nucleic acid molecule encoding a HSP. In this embodiment, it is preferred that the polypeptide be encoded by an allelic variant of a gene that encodes a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO: 410-611. More preferred is that the polypeptide be encoded by an allelic variant of a gene that has the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1-409.

Polypeptides of the present invention are also inclusive of derivative polypeptides encoded by a nucleic acid molecule according to the instant invention. In this

embodiment, it is preferred that the polypeptide be a HSP. Also preferred are derivative polypeptides having an amino acid sequence selected from the group consisting of SEQ ID NO: 410-611 and which has been acetylated, carboxylated, phosphorylated, glycosylated, ubiquitinated or other PTMs. In another preferred embodiment, the derivative has been labeled with, *e.g.*, radioactive isotopes such as  $^{125}\text{I}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , and  $^3\text{H}$ . In another preferred embodiment, the derivative has been labeled with fluorophores, chemiluminescent agents, enzymes, and antigens that can serve as specific binding pair members for a labeled ligand.

Polypeptide modifications are well known to those of skill and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as, for instance Creighton, Protein Structure and Molecular Properties, 2nd ed., W. H. Freeman and Company (1993). Many detailed reviews are available on this subject, such as, for example, those provided by Wold, in Johnson (ed.), Posttranslational Covalent Modification of Proteins, pgs. 1-12, Academic Press (1983); Seifter *et al.*, *Meth. Enzymol.* 182: 626-646 (1990) and Rattan *et al.*, *Ann. N.Y. Acad. Sci.* 663: 48-62 (1992).

One may determine whether a polypeptide of the invention is likely to be post-translationally modified by analyzing the sequence of the polypeptide to determine if there are peptide motifs indicative of sites for post-translational modification. There are a number of computer programs that permit prediction of post-translational modifications. See, *e.g.*, [www.expasy.org](http://www.expasy.org) (accessed November 11, 2002), which includes PSORT, for prediction of protein sorting signals and localization sites, SignalP, for prediction of signal peptide cleavage sites, MITOPROT and Predotar, for prediction of mitochondrial targeting sequences, NetOGlyc, for prediction of type O-glycosylation sites in mammalian proteins, big-PI Predictor and DGPI, for prediction of prenylation-anchor and cleavage sites, and NetPhos, for prediction of Ser, Thr and Tyr phosphorylation sites in eukaryotic proteins. Other computer programs, such as those included in GCG, also may be used to determine post-translational modification peptide motifs.

General examples of types of post-translational modifications include, but are not limited to: (Z)-dehydrobutyrine; 1-chondroitin sulfate-L-aspartic acid ester; 1'-glycosyl-L-tryptophan; 1'-phospho-L-histidine; 1-thioglycine; 2'-(S-L-cysteinyl)-L-histidine; 2'-[3-

carboxamido (trimethylammonio)propyl]-L-histidine; 2'-alpha-mannosyl-L-tryptophan; 2-methyl-L-glutamine; 2-oxobutanoic acid; 2-pyrrolidone carboxylic acid; 3'-(1'-L-histidyl)-L-tyrosine; 3'-(8alpha-FAD)-L-histidine; 3'-(S-L-cysteinyl)-L-tyrosine; 3', 3'', 5'-triiodo-L-tyrosine; 3'-4'-phospho-L-tyrosine; 3-hydroxy-L-proline; 3'-methyl-L-histidine; 3-

5 methyl-L-lanthionine; 3'-phospho-L-histidine; 4'-(L-tryptophan)-L-tryptophyl quinone; 42 N-cysteinyl-glycosylphosphatidylinositoethanolamine; 43 -(T-L-histidyl)-L-tyrosine; 4-hydroxy-L-arginine; 4-hydroxy-L-lysine; 4-hydroxy-L-proline; 5'-(N6-L-lysine)-L-topaquinone; 5-hydroxy-L-lysine; 5-methyl-L-arginine; alpha-I-microglobulin-Ig alpha complex chromophore; bis-L-cysteinyl bis-L-histidino diiron disulfide; bis-L--cysteinyl-L-

10 N3'-histidino-L-serinyl tetrairon' tetrasulfide; chondroitin sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-alanine; D-allo-isoleucine; D-asparagine; dehydroalanine; dehydrotyrosine; dermatan 4-sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-glucuronyl-N-glycine; dipyrrolylmethanemethyl-L-cysteine; D-leucine; D-methionine; D-phenylalanine; D-serine; D-tryptophan; glycine

15 amide; glycine oxazolecarboxylic acid; glycine thiazolecarboxylic acid; heme P450-bis-L-cysteine-L-tyrosine; heme-bis-L-cysteine; hemediol-L-aspartyl ester-L-glutamyl ester; hemediol-L-aspartyl ester-L-glutamyl ester-L-methionine sulfonium; heme-L-cysteine; heme-L-histidine; heparan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; heme P450-bis-L-cysteine-L-lysine; hexakis-L-cysteinyl hexairon hexasulfide;

20 keratan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-threonine; L-oxoalanine- lactic acid; L phenyllactic acid; l'-(8alpha-FAD)-L-histidine; L-2',4',5'-topaquinone; L-3',4'-dihydroxyphenylalanine; L-3'.4'.5'-trihydroxyphenylalanine; L-4'-bromophenylalanine; L-6'-bromotryptophan; L-alanine amide; L-alanyl imidazolinone glycine; L-allysine; L-arginine amide; L-asparagine amide; L-aspartic 4-phosphoric

25 anhydride; L-aspartic acid 1-amide; L-beta-methylthioaspartic acid; L-bromohistidine; L-citrulline; L-cysteine amide; L-cysteine glutathione disulfide; L-cysteine methyl disulfide; L-cysteine methyl ester; L-cysteine oxazolecarboxylic acid; L-cysteine oxazolinecarboxylic acid; L-cysteine persulfide; L-cysteine sulfenic acid; L-cysteine sulfinic acid; L-cysteine thiazolecarboxylic acid; L-cysteinyl homocitryl molybdenum-

30 heptairon-nonasulfide; L-cysteinyl imidazolinone glycine; L-cysteinyl molybdopterin; L-cysteinyl molybdopterin guanine dinucleotide; L-cystine; L-erythro-beta-hydroxyasparagine; L-erythro-beta-hydroxyaspartic acid; L-gamma-carboxyglutamic acid; L-glutamic acid 1-amide; L-glutamic acid 5-methyl ester; L-glutamine amide; L-glutamyl



- 5-glycerylphosphorylethanolamine; L-histidine amide; L-isoglutamyl-polyglutamic acid; L-isoglutamyl-polyglycine; L-isoleucine amide; L-lanthionine; L-leucine amide; L-lysine amide; L-lysine thiazolecarboxylic acid; L-lysinoalanine; L-methionine amide; L-methionine sulfone; L-phenylalanine thiazolecarboxylic acid; L-phenylalanine amide; L-proline amide; L-selenocysteine; L-selenocysteinyl molybdopterin guanine dinucleotide; L-serine amide; L-serine thiazolecarboxylic acid; L-seryl imidazolinone glycine; L-T-bromophenylalanine; L-T-bromophenylalanine; L-threonine amide; L-thyroxine; L-tryptophan amide; L-tryptophyl quinone; L-tyrosine amide; L-valine amide; meso-lanthionine; N-(L-glutamyl)-L-tyrosine; N-(L-isoaspartyl)-glycine; N-(L-isoaspartyl)-L-cysteine; N,N,N-trimethyl-L-alanine; N,N-dimethyl-L-proline; N2-acetyl-L-lysine; N2-succinyl-L-tryptophan; N4-(ADP-ribosyl)-L-asparagine; N4-glycosyl-L-asparagine; N4-hydroxymethyl-L-asparagine; N4-methyl-L-asparagine; N5-methyl-L-glutamine; N6-1-carboxyethyl-L-lysine; N6-(4-amino hydroxybutyl)-L-lysine; N6-(L-isoglutamyl)-L-lysine; N6-(phospho-5'-adenosine)-L-lysine; N6-(phospho-5'-guanosine)-L-lysine; N6,N6,N6-trimethyl-L-lysine; N6,N6-dimethyl-L-lysine; N6-acetyl-L-lysine; N6-biotinyl-L-lysine; N6-carboxy-L-lysine; N6-formyl-L-lysine; N6-glycyl-L-lysine; N6-lipoyl-L-lysine; N6-methyl-L-lysine; N6-methyl-N6-poly(N-methyl-propylamine)-L-lysine; N6-mureinyl-L-lysine; N6-myristoyl-L-lysine; N6-palmitoyl-L-lysine; N6-pyridoxal phosphate-L-lysine; N6-pyruvic acid 2-iminyl-L-lysine; N6-retinal-L-lysine; N-acetyl-glycine; N-acetyl-L-glutamine; N-acetyl-L-alanine; N-acetyl-L-aspartic acid; N-acetyl-L-cysteine; N-acetyl-L-glutamic acid; N-acetyl-L-isoleucine; N-acetyl-L-methionine; N-acetyl-L-proline; N-acetyl-L-serine; N-acetyl-L-threonine; N-acetyl-L-tyrosine; N-acetyl-L-valine; N-alanyl-glycosylphosphatidylinositoethanolamine; N-asparaginyl-glycosylphosphatidylinositoethanolamine; N-aspartyl-glycosylphosphatidylinositoethanolamine; N-formylglycine; N-formyl-L-methionine; N-glycyl-glycosylphosphatidylinositoethanolamine; N-L-glutamyl-poly-L-glutamic acid; N-methylglycine; N-methyl-L-alanine; N-methyl-L-methionine; N-methyl-L-phenylalanine; N-myristoyl-glycine; N-palmitoyl-L-cysteine; N-pyruvic acid 2-iminyl-L-cysteine; N-pyruvic acid 2-iminyl-L-valine; N-seryl-glycosylphosphatidylinositoethanolamine; N-seryl-glycosylHSPHINGOLIPIDINOSITOETHANOLAMINE; O-(ADP-ribosyl)-L-serine; O-(phospho-5'-adenosine)-L-threonine; O-(phospho-5'-DNA)-L-serine; O-(phospho-5'-DNA)-L-threonine; O-(phospho-5'tRNA)-L-serine; O-(phosphoribosyl dephospho-coenzyme A)-L-serine; O-(sn-1-glycerophosphoryl)-L-serine; O4'-(8alpha-FAD)-L-tyrosine; O4'-(phospho-

5'-adenosine)-L-tyrosine; O4'-(phospho-5'-DNA)-L-tyrosine; O4'-(phospho-5'-RNA)-L-tyrosine; O4'-(phospho-5'-uridine)-L-tyrosine; O4'-glycosyl-L-hydroxyproline; O4'-glycosyl-L-tyrosine; O4'-sulfo-L-tyrosine; O5-glycosyl-L-hydroxylysine; O-glycosyl-L-serine; O-glycosyl-L-threonine; omega-N-(ADP-ribosyl)-L-arginine; omega-N-omega-N'-dimethyl-L-arginine; omega-N-methyl-L-arginine; omega-N-omega-N-dimethyl-L-arginine; omega-N-phospho-L-arginine; O'-octanoyl-L-serine; O-palmitoyl-L-serine; O-palmitoyl-L-threonine; O-phospho-L-serine; O-phospho-L-threonine; O-phosphopantetheine-L-serine; phycoerythrobilin-bis-L-cysteine; phycourobilin-bis-L-cysteine; pyrroloquinoline quinone; pyruvic acid; S-hydroxycinnamyl-L-cysteine; S-(2-aminovinyl)-methyl-D-cysteine; S-(2-aminovinyl)-D-cysteine; S-(6-FW)-L-cysteine; S-(8alpha-FAD)-L-cysteine; S-(ADP-ribosyl)-L-cysteine; S-(L-isoglutamyl)-L-cysteine; S-12-hydroxyfarnesyl-L-cysteine; S-acetyl-L-cysteine; S-diacylglycerol-L-cysteine; S-diphytanylglycerol-diether-L-cysteine; S-farnesyl-L-cysteine; S-geranylgeranyl-L-cysteine; S-glycosyl-L-cysteine; S-glycyl-L-cysteine; S-methyl-L-cysteine; S-nitrosyl-L-cysteine; S-palmitoyl-L-cysteine; S-phospho-L-cysteine; S-phycobiliviolin-L-cysteine; S-phycocyanobilin-L-cysteine; S-phycoerythrobilin-L-cysteine; S-phytochromobilin-L-cysteine; S-selenyl-L-cysteine; S-sulfo-L-cysteine; tetrakis-L-cysteinyl-diiron disulfide; tetrakis-L-cysteinyl-iron; tetrakis-L-cysteinyl-tetrairon tetrasulfide; trans-2,3-cis-4-dihydroxy-L-proline; tris-L-cysteinyl-triiron tetrasulfide; tris-L-cysteinyl-triiron trisulfide; tris-L-cysteinyl-L-aspartato-tetrairon tetrasulfide; tris-L-cysteinyl-L-cysteine persulfido-bis-L-glutamato-L-histidino-tetrairon disulfide trioxide; tris-L-cysteinyl-L-N3'-histidino-tetrairon tetrasulfide; tris-L-cysteinyl-L-N1'-histidino-tetrairon tetrasulfide; and tris-L-cysteinyl-L-serinyl-tetrairon tetrasulfide.

Additional examples of PTMs may be found in web sites such as the Delta Mass database based on Krishna, R. G. and F. Wold (1998). Posttranslational Modifications. Proteins - Analysis and Design. R. H. Angeletti. San Diego, Academic Press. 1: 121-206. ; Methods in Enzymology, 193, J.A. McClosky (ed) (1990), pages 647-660; Methods in Protein Sequence Analysis edited by Kazutomo Imahori and Fumio Sakiyama, Plenum Press, (1993) "Post-translational modifications of proteins" R.G. Krishna and F. Wold pages 167-172; "GlycoSuiteDB: a new curated relational database of glycoprotein glycan structures and their biological sources" Cooper et al. Nucleic Acids Res. 29; 332-335 (2001) "O-GLYCBASE version 4.0: a revised database of O-glycosylated proteins" Gupta et al. Nucleic Acids Research, 27: 370-372 (1999); and "PhosphoBase, a database of

phosphorylation sites: release 2.0.", Kreegipuu et al. *Nucleic Acids Res* 27(1):237-239 (1999) see also, WO 02/21139A2, the disclosure of which is incorporated herein by reference in its entirety.

Tumorigenesis is often accompanied by alterations in the post-translational  
5 modifications of proteins. Thus, in another embodiment, the invention provides polypeptides from cancerous cells or tissues that have altered post-translational modifications compared to the post-translational modifications of polypeptides from normal cells or tissues. A number of altered post-translational modifications are known. One common alteration is a change in phosphorylation state, wherein the polypeptide from  
10 the cancerous cell or tissue is hyperphosphorylated or hypophosphorylated compared to the polypeptide from a normal tissue, or wherein the polypeptide is phosphorylated on different residues than the polypeptide from a normal cell. Another common alteration is a change in glycosylation state, wherein the polypeptide from the cancerous cell or tissue has more or less glycosylation than the polypeptide from a normal tissue, and/or wherein  
15 the polypeptide from the cancerous cell or tissue has a different type of glycosylation than the polypeptide from a noncancerous cell or tissue. Changes in glycosylation may be critical because carbohydrate-protein and carbohydrate-carbohydrate interactions are important in cancer cell progression, dissemination and invasion. See, e.g., Barchi, *Curr. Pharm. Des.* 6: 485-501 (2000), Verma, *Cancer Biochem. Biophys.* 14: 151-162 (1994)  
20 and Dennis et al., *Bioessays* 5: 412-421 (1999).

Another post-translational modification that may be altered in cancer cells is prenylation. Prenylation is the covalent attachment of a hydrophobic prenyl group (either farnesyl or geranylgeranyl) to a polypeptide. Prenylation is required for localizing a protein to a cell membrane and is often required for polypeptide function. For instance,  
25 the Ras superfamily of GTPase signalling proteins must be prenylated for function in a cell. See, e.g., Prendergast et al., *Semin. Cancer Biol.* 10: 443-452 (2000) and Khwaja et al., *Lancet* 355: 741-744 (2000).

Other post-translation modifications that may be altered in cancer cells include, without limitation, polypeptide methylation, acetylation, arginylation or racemization of  
30 amino acid residues. In these cases, the polypeptide from the cancerous cell may exhibit either increased or decreased amounts of the post-translational modification compared to the corresponding polypeptides from noncancerous cells.

Other polypeptide alterations in cancer cells include abnormal polypeptide cleavage of proteins and aberrant protein-protein interactions. Abnormal polypeptide cleavage may be cleavage of a polypeptide in a cancerous cell that does not usually occur in a normal cell, or a lack of cleavage in a cancerous cell, wherein the polypeptide is  
5 cleaved in a normal cell. Aberrant protein-protein interactions may be either covalent cross-linking or non-covalent binding between proteins that do not normally bind to each other. Alternatively, in a cancerous cell, a protein may fail to bind to another protein to which it is bound in a noncancerous cell. Alterations in cleavage or in protein-protein interactions may be due to over- or underproduction of a polypeptide in a cancerous cell  
10 compared to that in a normal cell, or may be due to alterations in post-translational modifications (see above) of one or more proteins in the cancerous cell. See, e.g., Henschen-Edman, *Ann. N.Y. Acad. Sci.* 936: 580-593 (2001).

Alterations in polypeptide post-translational modifications, as well as changes in polypeptide cleavage and protein-protein interactions, may be determined by any method  
15 known in the art. For instance, alterations in phosphorylation may be determined by using anti-phosphoserine, anti-phosphothreonine or anti-phosphotyrosine antibodies or by amino acid analysis. Glycosylation alterations may be determined using antibodies specific for different sugar residues, by carbohydrate sequencing, or by alterations in the size of the glycoprotein, which can be determined by, e.g., SDS polyacrylamide gel electrophoresis  
20 (PAGE). Other alterations of post-translational modifications, such as prenylation, racemization, methylation, acetylation and arginylation, may be determined by chemical analysis, protein sequencing, amino acid analysis, or by using antibodies specific for the particular post-translational modifications. Changes in protein-protein interactions and in polypeptide cleavage may be analyzed by any method known in the art including, without  
25 limitation, non-denaturing PAGE (for non-covalent protein-protein interactions), SDS PAGE (for covalent protein-protein interactions and protein cleavage), chemical cleavage, protein sequencing or immunoassays.

In another embodiment, the invention provides polypeptides that have been post-translationally modified. In one embodiment, polypeptides may be modified  
30 enzymatically or chemically, by addition or removal of a post-translational modification. For example, a polypeptide may be glycosylated or deglycosylated enzymatically. Similarly, polypeptides may be phosphorylated using a purified kinase, such as a MAP kinase (e.g., p38, ERK, or JNK) or a tyrosine kinase (e.g., Src or erbB2). A polypeptide

may also be modified through synthetic chemistry. Alternatively, one may isolate the polypeptide of interest from a cell or tissue that expresses the polypeptide with the desired post-translational modification. In another embodiment, a nucleic acid molecule encoding the polypeptide of interest is introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide in the desired fashion. If the polypeptide does not contain a motif for a desired post-translational modification, one may alter the post-translational modification by mutating the nucleic acid sequence of a nucleic acid molecule encoding the polypeptide so that it contains a site for the desired post-translational modification. Amino acid sequences that may be post-translationally modified are known in the art. See, e.g., the programs described above on the website [www.expasy.org](http://www.expasy.org). The nucleic acid molecule may also be introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide. Similarly, one may delete sites that are post-translationally modified by either mutating the nucleic acid sequence so that the encoded polypeptide does not contain the post-translational modification motif, or by introducing the native nucleic acid molecule into a host cell that is not capable of post-translationally modifying the encoded polypeptide.

It will be appreciated, as is well known and as noted above, that polypeptides are not always entirely linear. For instance, polypeptides may be branched as a result of ubiquitination, and they may be circular, with or without branching, generally as a result of posttranslation events, including natural processing event and events brought about by human manipulation which do not occur naturally. Circular, branched and branched circular polypeptides may be synthesized by non-translation natural process and by entirely synthetic methods, as well. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. In fact, blockage of the amino or carboxyl group in a polypeptide, or both, by a covalent modification, is common in naturally occurring and synthetic polypeptides and such modifications may be present in polypeptides of the present invention, as well. For instance, the amino terminal residue of polypeptides made in *E. coli*, prior to proteolytic processing, almost invariably will be N-formylmethionine.

Useful post-synthetic (and post-translational) modifications include conjugation to detectable labels, such as fluorophores. A wide variety of amine-reactive and thiol-reactive fluorophore derivatives have been synthesized that react under nondenaturing

conditions with N-terminal amino groups and epsilon amino groups of lysine residues, on the one hand, and with free thiol groups of cysteine residues, on the other.

Kits are available commercially that permit conjugation of proteins to a variety of amine-reactive or thiol-reactive fluorophores: Molecular Probes, Inc. (Eugene, OR, USA),  
 5 *e.g.*, offers kits for conjugating proteins to Alexa Fluor 350, Alexa Fluor 430, Fluorescein-EX, Alexa Fluor 488, Oregon Green 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, and Texas Red-X.

A wide variety of other amine-reactive and thiol-reactive fluorophores are available commercially (Molecular Probes, Inc., Eugene, OR, USA), including Alexa  
 10 Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY  
 15 TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA).

The polypeptides of the present invention can also be conjugated to fluorophores,  
 20 other proteins, and other macromolecules, using bifunctional linking reagents. Common homobifunctional reagents include, *e.g.*, APG, AEDP, BASED, BMB, BMDB, BMH, BMOE, BM[PEO]3, BM[PEO]4, BS3, BSOE, DFDNB, DMA, DMP, DMS, DPDPB, DSG, DSP (Lomant's Reagent), DSS, DST, DTBP, DTME, DTSSP, EGS, HBVS, Sulfo-BSOE, Sulfo-DST, Sulfo-EGS (all available from Pierce, Rockford, IL, USA);  
 25 common heterobifunctional cross-linkers include ABH, AMAS, ANB-NOS, APDP, ASBA, BMAP, BMPH, BMPS, EDC, EMCA, EMCH, EMCS, KMUA, KMH, GMBS, LC-SMCC, LC-SPDP, MBS, M2C2H, MPBH, MSA, NHS-ASA, PDPH, PMPI, SADP, SAED, SAND, SANPAH, SASD, SATP, SBAP, SFAD, SIA, SIAB, SMCC, SMPB, SMPH, SMPT, SPDP, Sulfo-EMCS, Sulfo-GMBS, Sulfo-HSAB, Sulfo-KMUS,  
 30 Sulfo-LC-SPDP, Sulfo-MBS, Sulfo-NHS-LC-ASA, Sulfo-SADP, Sulfo-SANPAH, Sulfo-SIAB, Sulfo-SMCC, Sulfo-SMPB, Sulfo-LC-SMPT, SVSB, TFCS (all available from Pierce, Rockford, IL, USA).

Polypeptides of the present invention, including full length polypeptides, fragments and fusion proteins, can be conjugated, using such cross-linking reagents, to fluorophores that are not amine- or thiol-reactive. Other labels that usefully can be conjugated to polypeptides of the present invention include radioactive labels, echosonographic contrast reagents, and MRI contrast agents.

Polypeptides of the present invention, including full length polypeptide, fragments and fusion proteins, can also usefully be conjugated using cross-linking agents to carrier proteins, such as KLH, bovine thyroglobulin, and even bovine serum albumin (BSA), to increase immunogenicity for raising anti-HSP antibodies.

Polypeptides of the present invention, including full length polypeptide, fragments and fusion proteins, can also usefully be conjugated to polyethylene glycol (PEG); PEGylation increases the serum half life of proteins administered intravenously for replacement therapy. Delgado *et al.*, *Crit. Rev. Ther. Drug Carrier Syst.* 9(3-4): 249-304 (1992); Scott *et al.*, *Curr. Pharm. Des.* 4(6): 423-38 (1998); DeSantis *et al.*, *Curr. Opin. Biotechnol.* 10(4): 324-30 (1999). PEG monomers can be attached to the protein directly or through a linker, with PEGylation using PEG monomers activated with tresyl chloride (2,2,2-trifluoroethanesulphonyl chloride) permitting direct attachment under mild conditions.

Polypeptides of the present invention are also inclusive of analogs of a polypeptide encoded by a nucleic acid molecule according to the instant invention. In a preferred embodiment, this polypeptide is a HSP. In a more preferred embodiment, this polypeptide is derived from a polypeptide having part or all of the amino acid sequence of SEQ ID NO: 410-611. Also preferred is an analog polypeptide comprising one or more substitutions of non-natural amino acids or non-native inter-residue bonds compared to the naturally occurring polypeptide. In one embodiment, the analog is structurally similar to a HSP, but one or more peptide linkages is replaced by a linkage selected from the group consisting of --CH<sub>2</sub>NH--, --CH<sub>2</sub>S--, --CH<sub>2</sub>-CH<sub>2</sub>--, --CH=CH--(cis and trans), --COCH<sub>2</sub>--, --CH(OH)CH<sub>2</sub>-- and --CH<sub>2</sub>SO--. In another embodiment, the analog comprises substitution of one or more amino acids of a HSP with a D-amino acid of the same type or other non-natural amino acid in order to generate more stable peptides. D-amino acids can readily be incorporated during chemical peptide synthesis: peptides assembled from D-amino acids are more resistant to proteolytic attack; incorporation of D-amino acids can

also be used to confer specific three-dimensional conformations on the peptide. Other amino acid analogues commonly added during chemical synthesis include ornithine, norleucine, phosphorylated amino acids (typically phosphoserine, phosphothreonine, phosphotyrosine), L-malonyltyrosine, a non-hydrolyzable analog of phosphotyrosine (*see*,  
5 *e.g.*, Kole *et al.*, *Biochem. Biophys. Res. Com.* 209: 817-821 (1995)), and various halogenated phenylalanine derivatives.

Non-natural amino acids can be incorporated during solid phase chemical synthesis or by recombinant techniques, although the former is typically more common. Solid phase chemical synthesis of peptides is well established in the art. Procedures are  
10 described, *inter alia*, in Chan *et al.* (eds.), Fmoc Solid Phase Peptide Synthesis: A Practical Approach (Practical Approach Series), Oxford Univ. Press (March 2000); Jones, Amino Acid and Peptide Synthesis (Oxford Chemistry Primers, No 7), Oxford Univ. Press (1992); and Bodanszky, Principles of Peptide Synthesis (Springer Laboratory), Springer Verlag (1993).

15 Amino acid analogues having detectable labels are also usefully incorporated during synthesis to provide derivatives and analogs. Biotin, for example can be added using biotinoyl--(9-fluorenylmethoxycarbonyl)-L-lysine (Fmoc biocytin) (Molecular Probes, Eugene, OR, USA). Biotin can also be added enzymatically by incorporation into a fusion protein of a *E. coli* BirA substrate peptide. The Fmoc and *t*BOC derivatives of  
20 dabcyl-L-lysine (Molecular Probes, Inc., Eugene, OR, USA) can be used to incorporate the dabcyl chromophore at selected sites in the peptide sequence during synthesis. The aminonaphthalene derivative EDANS, the most common fluorophore for pairing with the dabcyl quencher in fluorescence resonance energy transfer (FRET) systems, can be introduced during automated synthesis of peptides by using EDANS--Fmoc-L-glutamic  
25 acid or the corresponding *t*BOC derivative (both from Molecular Probes, Inc., Eugene, OR, USA). Tetramethylrhodamine fluorophores can be incorporated during automated Fmoc synthesis of peptides using (Fmoc)--TMR-L-lysine (Molecular Probes, Inc. Eugene, OR, USA).

Other useful amino acid analogues that can be incorporated during chemical  
30 synthesis include aspartic acid, glutamic acid, lysine, and tyrosine analogues having allyl side-chain protection (Applied Biosystems, Inc., Foster City, CA, USA); the allyl side chain permits synthesis of cyclic, branched-chain, sulfonated, glycosylated, and phosphorylated peptides.



A large number of other Fmoc-protected non-natural amino acid analogues capable of incorporation during chemical synthesis are available commercially, including, e.g., Fmoc-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid, Fmoc-3-endo-aminobicyclo[2.2.1]heptane-2-endo-carboxylic acid, Fmoc-3-exo-aminobicyclo[2.2.1]heptane-2-exo-carboxylic acid, Fmoc-3-endo-amino-bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid, Fmoc-3-exo-amino-bicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid, Fmoc-cis-2-amino-1-cyclohexanecarboxylic acid, Fmoc-trans-2-amino-1-cyclohexanecarboxylic acid, Fmoc-1-amino-1-cyclopentanecarboxylic acid, Fmoc-cis-2-amino-1-cyclopentanecarboxylic acid, Fmoc-1-amino-1-cyclopropanecarboxylic acid, Fmoc-D-2-amino-4-(ethylthio)butyric acid, Fmoc-L-2-amino-4-(ethylthio)butyric acid, Fmoc-L-buthionine, Fmoc-S-methyl-L-Cysteine, Fmoc-2-aminobenzoic acid (anthranillic acid), Fmoc-3-aminobenzoic acid, Fmoc-4-aminobenzoic acid, Fmoc-2-aminobenzophenone-2'-carboxylic acid, Fmoc-N-(4-aminobenzoyl)- $\beta$ -alanine, Fmoc-2-amino-4,5-dimethoxybenzoic acid, Fmoc-4-aminohippuric acid, Fmoc-2-amino-3-hydroxybenzoic acid, Fmoc-2-amino-5-hydroxybenzoic acid, Fmoc-3-amino-4-hydroxybenzoic acid, Fmoc-4-amino-3-hydroxybenzoic acid, Fmoc-4-amino-2-hydroxybenzoic acid, Fmoc-5-amino-2-hydroxybenzoic acid, Fmoc-2-amino-3-methoxybenzoic acid, Fmoc-4-amino-3-methoxybenzoic acid, Fmoc-2-amino-3-methylbenzoic acid, Fmoc-2-amino-5-methylbenzoic acid, Fmoc-2-amino-6-methylbenzoic acid, Fmoc-3-amino-2-methylbenzoic acid, Fmoc-3-amino-4-methylbenzoic acid, Fmoc-4-amino-3-methylbenzoic acid, Fmoc-3-amino-2-naphtoic acid, Fmoc-D,L-3-amino-3-phenylpropionic acid, Fmoc-L-Methyldopa, Fmoc-2-amino-4,6-dimethyl-3-pyridinecarboxylic acid, Fmoc-D,L-amino-2-thiophenacetic acid, Fmoc-4-(carboxymethyl)piperazine, Fmoc-4-carboxypiperazine, Fmoc-4-(carboxymethyl)homopiperazine, Fmoc-4-phenyl-4-piperidinecarboxylic acid, Fmoc-L-1,2,3,4-tetrahydronorharman-3-carboxylic acid, Fmoc-L-thiazolidine-4-carboxylic acid, all available from The Peptide Laboratory (Richmond, CA, USA).

Non-natural residues can also be added biosynthetically by engineering a suppressor tRNA, typically one that recognizes the UAG stop codon, by chemical aminoacylation with the desired unnatural amino acid. Conventional site-directed mutagenesis is used to introduce the chosen stop codon UAG at the site of interest in the protein gene. When the acylated suppressor tRNA and the mutant gene are combined in

an *in vitro* transcription/translation system, the unnatural amino acid is incorporated in response to the UAG codon to give a protein containing that amino acid at the specified position. Liu *et al.*, *Proc. Natl Acad. Sci. USA* 96(9): 4780-5 (1999); Wang *et al.*, *Science* 292(5516): 498-500 (2001).

5           *Fusion Proteins*

Another aspect of the present invention relates to the fusion of a polypeptide of the present invention to heterologous polypeptides. In a preferred embodiment, the polypeptide of the present invention is a HSP. In a more preferred embodiment, the polypeptide of the present invention that is fused to a heterologous polypeptide comprises  
10   part or all of the amino acid sequence of SEQ ID NO: 410-611, or is a mutein, homologous polypeptide, analog or derivative thereof. In an even more preferred embodiment, the fusion protein is encoded by a nucleic acid molecule comprising all or part of the nucleic acid sequence of SEQ ID NO: 1-409, or comprises all or part of a nucleic acid sequence that selectively hybridizes or is homologous to a nucleic acid  
15   molecule comprising a nucleic acid sequence of SEQ ID NO: 1-409.

The fusion proteins of the present invention will include at least one fragment of a polypeptide of the present invention, which fragment is at least 6, typically at least 8, often at least 15, and usefully at least 16, 17, 18, 19, or 20 amino acids long. The fragment of the polypeptide of the present to be included in the fusion can usefully be at least 25  
20   amino acids long, at least 50 amino acids long, and can be at least 75, 100, or even 150 amino acids long. Fusions that include the entirety of a polypeptide of the present invention have particular utility.

The heterologous polypeptide included within the fusion protein of the present invention is at least 6 amino acids in length, often at least 8 amino acids in length, and  
25   preferably at least 15, 20, or 25 amino acids in length. Fusions that include larger polypeptides, such as the IgG Fc region, and even entire proteins (such as GFP chromophore-containing proteins) are particularly useful.

As described above in the description of vectors and expression vectors of the present invention, which discussion is incorporated here by reference in its entirety,  
30   heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those designed to facilitate purification and/or visualization of recombinantly-expressed proteins. See, e.g., Ausubel, Chapter 16, (1992), *supra*.

Although purification tags can also be incorporated into fusions that are chemically synthesized, chemical synthesis typically provides sufficient purity that further purification by HPLC suffices; however, visualization tags as above described retain their utility even when the protein is produced by chemical synthesis, and when so included  
5 render the fusion proteins of the present invention useful as directly detectable markers of the presence of a polypeptide of the invention.

As also discussed above, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those that facilitate secretion of recombinantly expressed proteins into the periplasmic space or extracellular milieu for  
10 prokaryotic hosts or into the culture medium for eukaryotic cells through incorporation of secretion signals and/or leader sequences. For example, a His<sup>6</sup> tagged protein can be purified on a Ni affinity column and a GST fusion protein can be purified on a glutathione affinity column. Similarly, a fusion protein comprising the Fc domain of IgG can be purified on a Protein A or Protein G column and a fusion protein comprising an epitope  
15 tag such as myc can be purified using an immunoaffinity column containing an anti-c-myc antibody. It is preferable that the epitope tag be separated from the protein encoded by the essential gene by an enzymatic cleavage site that can be cleaved after purification. See also the discussion of nucleic acid molecules encoding fusion proteins that may be expressed on the surface of a cell.

20 Other useful fusion proteins of the present invention include those that permit use of the polypeptide of the present invention as bait in a yeast two-hybrid system. See Bartel *et al.* (eds.), The Yeast Two-Hybrid System, Oxford University Press (1997); Zhu *et al.*, Yeast Hybrid Technologies, Eaton Publishing (2000); Fields *et al.*, *Trends Genet.* 10(8): 286-92 (1994); Mendelsohn *et al.*, *Curr. Opin. Biotechnol.* 5(5): 482-6 (1994);  
25 Luban *et al.*, *Curr. Opin. Biotechnol.* 6(1): 59-64 (1995); Allen *et al.*, *Trends Biochem. Sci.* 20(12): 511-6 (1995); Drees, *Curr. Opin. Chem. Biol.* 3(1): 64-70 (1999); Topcu *et al.*, *Pharm. Res.* 17(9): 1049-55 (2000); Fashena *et al.*, *Gene* 250(1-2): 1-14 (2000); Colas *et al.*, *Nature* 380, 548-550 (1996); Norman, T. *et al.*, *Science* 285, 591-595 (1999); Fabbri *et al.*, *Oncogene* 18, 4357-4363 (1999); Xu *et al.*, *Proc Natl Acad Sci U S A.*  
30 94, 12473-12478 (1997); Yang, *et al.*, *Nuc. Acids Res.* 23, 1152-1156 (1995); Kolonin *et al.*, *Proc Natl Acad Sci U S A* 95, 14266-14271 (1998); Cohen *et al.*, *Proc Natl Acad Sci U S A* 95, 14272-14277 (1998); Uetz, *et al.* *Nature* 403, 623-627(2000); Ito, *et al.*, *Proc Natl Acad Sci U S A* 98, 4569-4574 (2001). Typically, such fusion is to either *E. coli* LexA or

yeast GAL4 DNA binding domains. Related bait plasmids are available that express the bait fused to a nuclear localization signal.

Other useful fusion proteins include those that permit display of the encoded polypeptide on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, such as green fluorescent protein (GFP), and fusions to the IgG Fc region, as described above.

The polypeptides of the present invention can also usefully be fused to protein toxins, such as *Pseudomonas* exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin lethal factor, ricin, in order to effect ablation of cells that bind or take up the proteins of the present invention.

Fusion partners include, *inter alia*, *myc*, hemagglutinin (HA), GST, immunoglobulins,  $\beta$ -galactosidase, biotin trpE, protein A,  $\beta$ -lactamase,  $\alpha$ -amylase, maltose binding protein, alcohol dehydrogenase, polyhistidine (for example, six histidine at the amino and/or carboxyl terminus of the polypeptide), lacZ, green fluorescent protein (GFP), yeast  $\alpha$  mating factor, GAL4 transcription activation or DNA binding domain, luciferase, and serum proteins such as ovalbumin, albumin and the constant domain of IgG. *See, e.g.*, Ausubel (1992), *supra* and Ausubel (1999), *supra*. Fusion proteins may also contain sites for specific enzymatic cleavage, such as a site that is recognized by enzymes such as Factor XIII, trypsin, pepsin, or any other enzyme known in the art. Fusion proteins will typically be made by either recombinant nucleic acid methods, as described above, chemically synthesized using techniques well known in the art (*e.g.*, a Merrifield synthesis), or produced by chemical cross-linking.

Another advantage of fusion proteins is that the epitope tag can be used to bind the fusion protein to a plate or column through an affinity linkage for screening binding proteins or other molecules that bind to the HSP.

As further described below, the polypeptides of the present invention can readily be used as specific immunogens to raise antibodies that specifically recognize polypeptides of the present invention including HSPs and their allelic variants and homologues. The antibodies, in turn, can be used, *inter alia*, specifically to assay for the polypeptides of the present invention, particularly HSPs, *e.g.* by ELISA for detection of protein fluid samples, such as serum, by immunohistochemistry or laser scanning cytometry, for detection of protein in tissue samples, or by flow cytometry, for detection of intracellular protein in cell suspensions, for specific antibody-mediated isolation and/or

purification of HSPs, as for example by immunoprecipitation, and for use as specific agonists or antagonists of HSPs.

One may determine whether polypeptides of the present invention including HSPs, mureins, homologous proteins or allelic variants or fusion proteins of the present invention  
5 are functional by methods known in the art. For instance, residues that are tolerant of change while retaining function can be identified by altering the polypeptide at known residues using methods known in the art, such as alanine scanning mutagenesis, Cunningham *et al.*, *Science* 244(4908): 1081-5 (1989); transposon linker scanning mutagenesis, Chen *et al.*, *Gene* 263(1-2): 39-48 (2001); combinations of homolog- and  
10 alanine-scanning mutagenesis, Jin *et al.*, *J. Mol. Biol.* 226(3): 851-65 (1992); combinatorial alanine scanning, Weiss *et al.*, *Proc. Natl. Acad. Sci USA* 97(16): 8950-4 (2000), followed by functional assay. Transposon linker scanning kits are available commercially (New England Biolabs, Beverly, MA, USA, catalog. no. E7-102S; EZ::TN™ In-Frame Linker Insertion Kit, catalogue no. EZI04KN, (Epicentre  
15 Technologies Corporation, Madison, WI, USA).

Purification of the polypeptides or fusion proteins of the present invention is well known and within the skill of one having ordinary skill in the art. *See, e.g.*, Scopes, Protein Purification, 2d ed. (1987). Purification of recombinantly expressed polypeptides is described above. Purification of chemically-synthesized peptides can readily be  
20 effected, *e.g.*, by HPLC.

Accordingly, it is an aspect of the present invention to provide the isolated polypeptides or fusion proteins of the present invention in pure or substantially pure form in the presence of absence of a stabilizing agent. Stabilizing agents include both proteinaceous and non-proteinaceous material and are well known in the art. Stabilizing  
25 agents, such as albumin and polyethylene glycol (PEG) are known and are commercially available.

Although high levels of purity are preferred when the isolated polypeptide or fusion protein of the present invention are used as therapeutic agents, such as in vaccines and replacement therapy, the isolated polypeptides of the present invention are also useful  
30 at lower purity. For example, partially purified polypeptides of the present invention can be used as immunogens to raise antibodies in laboratory animals.

In a preferred embodiment, the purified and substantially purified polypeptides of the present invention are in compositions that lack detectable ampholytes, acrylamide monomers, bis-acrylamide monomers, and polyacrylamide.

The polypeptides or fusion proteins of the present invention can usefully be  
5 attached to a substrate. The substrate can be porous or solid, planar or non-planar; the bond can be covalent or noncovalent. For example, the peptides of the invention may be stabilized by covalent linkage to albumin. See, U.S. Patent No. 5,876,969, the contents of which are hereby incorporated in its entirety.

For example, the polypeptides or fusion proteins of the present invention can  
10 usefully be bound to a porous substrate, commonly a membrane, typically comprising nitrocellulose, polyvinylidene fluoride (PVDF), or cationically derivatized, hydrophilic PVDF; so bound, the polypeptides or fusion proteins of the present invention can be used to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized polypeptide or fusion protein of the present invention.

15 As another example, the polypeptides or fusion proteins of the present invention can usefully be bound to a substantially nonporous substrate, such as plastic, to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized protein of the present invention. Such plastics include polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene,  
20 polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof; when the assay is performed in a standard microtiter dish, the plastic is typically polystyrene.

The polypeptides and fusion proteins of the present invention can also be attached to a substrate suitable for use as a surface enhanced laser desorption ionization source; so  
25 attached, the polypeptide or fusion protein of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biologic interaction there between. The polypeptides or fusion proteins of the present invention can also be attached to a substrate suitable for use in surface plasmon resonance detection; so attached, the  
30 polypeptide or fusion protein of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biological interaction there between.

### Antibodies

In another aspect, the invention provides antibodies, including fragments and derivatives thereof, that bind specifically to polypeptides encoded by the nucleic acid molecules of the invention. In a preferred embodiment, the antibodies are specific for a polypeptide that is a HSP, or a fragment, mutein, derivative, analog or fusion protein thereof. In a more preferred embodiment, the antibodies are specific for a polypeptide that comprises SEQ ID NO: 410-611, or a fragment, mutein, derivative, analog or fusion protein thereof.

The antibodies of the present invention can be specific for linear epitopes, discontinuous epitopes, or conformational epitopes of such proteins or protein fragments, either as present on the protein in its native conformation or, in some cases, as present on the proteins as denatured, as, *e.g.*, by solubilization in SDS. New epitopes may be also due to a difference in post translational modifications (PTMs) in disease versus normal tissue. For example, a particular site on a HSP may be glycosylated in cancerous cells, but not glycosylated in normal cells or vis versa. In addition, alternative splice forms of a HSP may be indicative of cancer. Differential degradation of the C or N-terminus of a HSP may also be a marker or target for anticancer therapy. For example, an HSP may be N-terminal degraded in cancer cells exposing new epitopes to which antibodies may selectively bind for diagnostic or therapeutic uses.

As is well known in the art, the degree to which an antibody can discriminate among molecular species in a mixture will depend, in part, upon the conformational relatedness of the species in the mixture; typically, the antibodies of the present invention will discriminate over adventitious binding to non-HSP polypeptides by at least two-fold, more typically by at least 5-fold, typically by more than 10-fold, 25-fold, 50-fold, 75-fold, and often by more than 100-fold, and on occasion by more than 500-fold or 1000-fold. When used to detect the proteins or protein fragments of the present invention, the antibody of the present invention is sufficiently specific when it can be used to determine the presence of the polypeptide of the present invention in samples derived from human hepatic.

Typically, the affinity or avidity of an antibody (or antibody multimer, as in the case of an IgM pentamer) of the present invention for a protein or protein fragment of the present invention will be at least about  $1 \times 10^{-6}$  molar (M), typically at least about  $5 \times 10^{-7}$

M,  $1 \times 10^{-7}$  M, with affinities and avidities of at least  $1 \times 10^{-8}$  M,  $5 \times 10^{-9}$  M,  $1 \times 10^{-10}$  M and up to  $1 \times 10^{-13}$  M proving especially useful.

The antibodies of the present invention can be naturally occurring forms, such as IgG, IgM, IgD, IgE, IgY, and IgA, from any avian, reptilian, or mammalian species.

5 Human antibodies can, but will infrequently, be drawn directly from human donors or human cells. In such case, antibodies to the polypeptides of the present invention will typically have resulted from fortuitous immunization, such as autoimmune immunization, with the polypeptide of the present invention. Such antibodies will typically, but will not invariably, be polyclonal. In addition, individual polyclonal antibodies may be isolated  
10 and cloned to generate monoclonals.

Human antibodies are more frequently obtained using transgenic animals that express human immunoglobulin genes, which transgenic animals can be affirmatively immunized with the protein immunogen of the present invention. Human Ig-transgenic mice capable of producing human antibodies and methods of producing human antibodies  
15 therefrom upon specific immunization are described, *inter alia*, in U.S. Patent Nos. 6,162,963; 6,150,584; 6,114,598; 6,075,181; 5,939,598; 5,877,397; 5,874,299; 5,814,318; 5,789,650; 5,770,429; 5,661,016; 5,633,425; 5,625,126; 5,569,825; 5,545,807; 5,545,806, and 5,591,669, the disclosures of which are incorporated herein by reference in their entirety. Such antibodies are typically monoclonal, and are typically produced using  
20 techniques developed for production of murine antibodies.

Human antibodies are particularly useful, and often preferred, when the antibodies of the present invention are to be administered to human beings as *in vivo* diagnostic or therapeutic agents, since recipient immune response to the administered antibody will often be substantially less than that occasioned by administration of an antibody derived  
25 from another species, such as mouse.

IgG, IgM, IgD, IgE, IgY, and IgA antibodies of the present invention are also usefully obtained from other species, including mammals such as rodents (typically mouse, but also rat, guinea pig, and hamster), lagomorphs (typically rabbits), and also larger mammals, such as sheep, goats, cows, and horses; or egg laying birds or reptiles  
30 such as chickens or alligators. In such cases, as with the transgenic human-antibody-producing non-human mammals, fortuitous immunization is not required, and the non-human mammal is typically affirmatively immunized, according to standard immunization



protocols, with the polypeptide of the present invention. One form of avian antibodies may be generated using techniques described in WO 00/29444, published 25 May 2000.

As discussed above, virtually all fragments of 8 or more contiguous amino acids of a polypeptide of the present invention can be used effectively as immunogens when  
5 conjugated to a carrier, typically a protein such as bovine thyroglobulin, keyhole limpet hemocyanin, or bovine serum albumin, conveniently using a bifunctional linker such as those described elsewhere above, which discussion is incorporated by reference here.

Immunogenicity can also be conferred by fusion of the polypeptide of the present invention to other moieties. For example, polypeptides of the present invention can be  
10 produced by solid phase synthesis on a branched polylysine core matrix; these multiple antigenic peptides (MAPs) provide high purity, increased avidity, accurate chemical definition and improved safety in vaccine development. Tam *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5409-5413 (1988); Posnett *et al.*, *J. Biol. Chem.* 263: 1719-1725 (1988).

Protocols for immunizing non-human mammals or avian species are well-  
15 established in the art. See Harlow *et al.* (eds.), Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory (1998); Coligan *et al.* (eds.), Current Protocols in Immunology, John Wiley & Sons, Inc. (2001); Zola, Monoclonal Antibodies: Preparation and Use of Monoclonal Antibodies and Engineered Antibody Derivatives (Basics: From Background to Bench), Springer Verlag (2000); Gross M, Speck *J.Dtsch. Tierarztl. Wochenschr.* 103: 417-422 (1996). Immunization protocols often include multiple  
20 immunizations, either with or without adjuvants such as Freund's complete adjuvant and Freund's incomplete adjuvant, and may include naked DNA immunization (Moss, *Semin. Immunol.* 2: 317-327 (1990)).

Antibodies from non-human mammals and avian species can be polyclonal or  
25 monoclonal, with polyclonal antibodies having certain advantages in immunohistochemical detection of the polypeptides of the present invention and monoclonal antibodies having advantages in identifying and distinguishing particular epitopes of the polypeptides of the present invention. Antibodies from avian species may have particular advantage in detection of the polypeptides of the present invention, in  
30 human serum or tissues (Vikinge *et al.*, *Biosens. Bioelectron.* 13: 1257-1262 (1998). Following immunization, the antibodies of the present invention can be obtained using any art-accepted technique. Such techniques are well known in the art and are described in detail in references such as Coligan, *supra*; Zola, *supra*; Howard *et al.* (eds.), Basic

Methods in Antibody Production and Characterization, CRC Press (2000); Harlow, *supra*; Davis (ed.), Monoclonal Antibody Protocols, Vol. 45, Humana Press (1995); Delves (ed.), Antibody Production: Essential Techniques, John Wiley & Son Ltd (1997); and Kenney, Antibody Solution: An Antibody Methods Manual, Chapman & Hall (1997).

5 Briefly, such techniques include, *inter alia*, production of monoclonal antibodies by hybridomas and expression of antibodies or fragments or derivatives thereof from host cells engineered to express immunoglobulin genes or fragments thereof. These two methods of production are not mutually exclusive: genes encoding antibodies specific for the polypeptides of the present invention can be cloned from hybridomas and thereafter  
10 expressed in other host cells. Nor need the two necessarily be performed together: *e.g.*, genes encoding antibodies specific for the polypeptides of the present invention can be cloned directly from B cells known to be specific for the desired protein, as further described in U.S. Patent No. 5,627,052, the disclosure of which is incorporated herein by reference in its entirety, or from antibody-displaying phage.

15 Recombinant expression in host cells is particularly useful when fragments or derivatives of the antibodies of the present invention are desired.

Host cells for recombinant antibody production of whole antibodies, antibody fragments, or antibody derivatives can be prokaryotic or eukaryotic.

20 Prokaryotic hosts are particularly useful for producing phage displayed antibodies of the present invention.

The technology of phage-displayed antibodies, in which antibody variable region fragments are fused, for example, to the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13, is by now well-established. *See, e.g.*, Sidhu, *Curr. Opin. Biotechnol.* 11(6): 610-6 (2000); Griffiths *et al.*, *Curr. Opin. Biotechnol.* 9(1): 102-8 (1998); Hoogenboom *et al.*, *Immunotechnology*, 4(1): 1-20 (1998);  
25 Rader *et al.*, *Current Opinion in Biotechnology* 8: 503-508 (1997); Aujame *et al.*, *Human Antibodies* 8: 155-168 (1997); Hoogenboom, *Trends in Biotechnol.* 15: 62-70 (1997); de Kruif *et al.*, 17: 453-455 (1996); Barbas *et al.*, *Trends in Biotechnol.* 14: 230-234 (1996); Winter *et al.*, *Ann. Rev. Immunol.* 433-455 (1994). Techniques and protocols required to  
30 generate, propagate, screen (pan), and use the antibody fragments from such libraries have recently been compiled. *See, e.g.*, Barbas (2001), *supra*; Kay, *supra*; and Abelson, *supra*.

Typically, phage-displayed antibody fragments are scFv fragments or Fab fragments; when desired, full length antibodies can be produced by cloning the variable

regions from the displaying phage into a complete antibody and expressing the full length antibody in a further prokaryotic or a eukaryotic host cell. Eukaryotic cells are also useful for expression of the antibodies, antibody fragments, and antibody derivatives of the present invention. For example, antibody fragments of the present invention can be  
5 produced in *Pichia pastoris* and in *Saccharomyces cerevisiae*. See, e.g., Takahashi *et al.*, *Biosci. Biotechnol. Biochem.* 64(10): 2138-44 (2000); Freyre *et al.*, *J. Biotechnol.* 76(2-3):1 57-63 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 117-20 (1999); Pennell *et al.*, *Res. Immunol.* 149(6): 599-603 (1998); Eldin *et al.*, *J. Immunol. Methods.* 201(1): 67-75 (1997);, Frenken *et al.*, *Res. Immunol.* 149(6): 589-99 (1998); and  
10 Shusta *et al.*, *Nature Biotechnol.* 16(8): 773-7 (1998).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in insect cells. See, e.g., Li *et al.*, *Protein Expr. Purif.* 21(1): 121-8 (2001); Ailor *et al.*, *Biotechnol. Bioeng.* 58(2-3): 196-203 (1998); Hsu *et al.*, *Biotechnol. Prog.* 13(1): 96-104 (1997); Edelman *et al.*, *Immunology* 91(1): 13-9 (1997); and Nesbit *et al.*, *J. Immunol. Methods* 151(1-2): 201-8 (1992).  
15

Antibodies and fragments and derivatives thereof of the present invention can also be produced in plant cells, particularly maize or tobacco, Giddings *et al.*, *Nature Biotechnol.* 18(11): 1151-5 (2000); Gavilondo *et al.*, *Biotechniques* 29(1): 128-38 (2000); Fischer *et al.*, *J. Biol. Regul. Homeost. Agents* 14(2): 83-92 (2000); Fischer *et al.*,  
20 *Biotechnol. Appl. Biochem.* 30 (Pt 2): 113-6 (1999); Fischer *et al.*, *Biol. Chem.* 380(7-8): 825-39 (1999); Russell, *Curr. Top. Microbiol. Immunol.* 240: 119-38 (1999); and Ma *et al.*, *Plant Physiol.* 109(2): 341-6 (1995).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in transgenic, non-human, mammalian milk. See, e.g. Pollock *et al.*,  
25 *J. Immunol Methods.* 231: 147-57 (1999); Young *et al.*, *Res. Immunol.* 149: 609-10 (1998); and Limonta *et al.*, *Immunotechnology* 1: 107-13 (1995).

Mammalian cells useful for recombinant expression of antibodies, antibody fragments, and antibody derivatives of the present invention include CHO cells, COS cells, 293 cells, and myeloma cells. Verma *et al.*, *J. Immunol. Methods* 216(1-2):165-81  
30 (1998) review and compare bacterial, yeast, insect and mammalian expression systems for expression of antibodies. Antibodies of the present invention can also be prepared by cell free translation, as further described in Merk *et al.*, *J. Biochem. (Tokyo)* 125(2): 328-33 (1999) and Ryabova *et al.*, *Nature Biotechnol.* 15(1): 79-84 (1997), and in the milk of

transgenic animals, as further described in Pollock *et al.*, *J. Immunol. Methods* 231(1-2): 147-57 (1999).

The invention further provides antibody fragments that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention. Among such useful fragments are Fab, Fab', Fv, F(ab')<sub>2</sub>, and single chain Fv (scFv) fragments. Other useful fragments are described in Hudson, *Curr. Opin. Biotechnol.* 9(4): 395-402 (1998).

The present invention also relates to antibody derivatives that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention.

Among such useful derivatives are chimeric, primatized, and humanized antibodies; such derivatives are less immunogenic in human beings, and thus are more suitable for *in vivo* administration, than are unmodified antibodies from non-human mammalian species. Another useful method is PEGylation to increase the serum half life of the antibodies.

Chimeric antibodies typically include heavy and/or light chain variable regions (including both CDR and framework residues) of immunoglobulins of one species, typically mouse, fused to constant regions of another species, typically human. *See, e.g.*, Morrison *et al.*, *Proc. Natl. Acad. Sci USA* 81(21): 6851-5 (1984); Sharon *et al.*, *Nature* 309(5966): 364-7 (1984); Takeda *et al.*, *Nature* 314(6010): 452-4 (1985); and U.S. Patent No. 5,807,715 the disclosure of which is incorporated herein by reference in its entirety. Primatized and humanized antibodies typically include heavy and/or light chain CDRs from a murine antibody grafted into a non-human primate or human antibody V region framework, usually further comprising a human constant region, Riechmann *et al.*, *Nature* 332(6162): 323-7 (1988); Co *et al.*, *Nature* 351(6326): 501-2 (1991); and U.S. Patent Nos. 6,054,297; 5,821,337; 5,770,196; 5,766,886; 5,821,123; 5,869,619; 6,180,377; 6,013,256; 5,693,761; and 6,180,370, the disclosures of which are incorporated herein by reference in

their entireties. Other useful antibody derivatives of the invention include heteromeric antibody complexes and antibody fusions, such as diabodies (bispecific antibodies), single-chain diabodies, and intrabodies.

It is contemplated that the nucleic acids encoding the antibodies of the present invention can be operably joined to other nucleic acids forming a recombinant vector for cloning or for expression of the antibodies of the invention. Accordingly, the present invention includes any recombinant vector containing the coding sequences, or part thereof, whether for eukaryotic transduction, transfection or gene therapy. Such vectors may be prepared using conventional molecular biology techniques, known to those with skill in the art, and would comprise DNA encoding sequences for the immunoglobulin V-regions including framework and CDRs or parts thereof, and a suitable promoter either with or without a signal sequence for intracellular transport. Such vectors may be transduced or transfected into eukaryotic cells or used for gene therapy (Marasco et al., *Proc. Natl. Acad. Sci. (USA)* 90: 7889-7893 (1993); Duan et al., *Proc. Natl. Acad. Sci. (USA)* 91: 5075-5079 (1994), by conventional techniques, known to those with skill in the art.

The antibodies of the present invention, including fragments and derivatives thereof, can usefully be labeled. It is, therefore, another aspect of the present invention to provide labeled antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention. The choice of label depends, in part, upon the desired use.

For example, when the antibodies of the present invention are used for immunohistochemical staining of tissue samples, the label can usefully be an enzyme that catalyzes production and local deposition of a detectable product. Enzymes typically conjugated to antibodies to permit their immunohistochemical visualization are well known, and include alkaline phosphatase,  $\beta$ -galactosidase, glucose oxidase, horseradish peroxidase (HRP), and urease. Typical substrates for production and deposition of visually detectable products include o-nitrophenyl-beta-D-galactopyranoside (ONPG); o-phenylenediamine dihydrochloride (OPD); p-nitrophenyl phosphate (PNPP); p-nitrophenyl-beta-D-galactopyranoside (PNPG); 3',3'-diaminobenzidine (DAB); 3-amino-

9-ethylcarbazole (AEC); 4-chloro-1-naphthol (CN);  
5-bromo-4-chloro-3-indolyl-phosphate (BCIP); ABTS®; BluoGal; iodonitrotetrazolium  
(INT); nitroblue tetrazolium chloride (NBT); phenazine methosulfate (PMS);  
phenolphthalein monophosphate (PMP); tetramethyl benzidine (TMB); tetranitroblue  
5 tetrazolium (TNBT); X-Gal; X-Gluc; and X-Glucoside.

Other substrates can be used to produce products for local deposition that are  
luminescent. For example, in the presence of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), horseradish  
peroxidase (HRP) can catalyze the oxidation of cyclic diacylhydrazides, such as luminol.  
Immediately following the oxidation, the luminol is in an excited state (intermediate  
10 reaction product), which decays to the ground state by emitting light. Strong enhancement  
of the light emission is produced by enhancers, such as phenolic compounds. Advantages  
include high sensitivity, high resolution, and rapid detection without radioactivity and  
requiring only small amounts of antibody. *See, e.g., Thorpe et al., Methods Enzymol.* 133:  
331-53 (1986); Kricka *et al., J. Immunoassay* 17(1): 67-83 (1996); and Lundqvist *et al., J.*  
15 *Biolumin. Chemilumin.* 10(6): 353-9 (1995). Kits for such enhanced chemiluminescent  
detection (ECL) are available commercially. The antibodies can also be labeled using  
colloidal gold.

As another example, when the antibodies of the present invention are used, *e.g., for*  
flow cytometric detection, for scanning laser cytometric detection, or for fluorescent  
20 immunoassay, they can usefully be labeled with fluorophores. There are a wide variety of  
fluorophore labels that can usefully be attached to the antibodies of the present invention.  
For flow cytometric applications, both for extracellular detection and for intracellular  
detection, common useful fluorophores can be fluorescein isothiocyanate (FITC),  
allophycocyanin (APC), R-phycoerythrin (PE), peridinin chlorophyll protein (PerCP),  
25 Texas Red, Cy3, Cy5, fluorescence resonance energy tandem fluorophores such as PerCP-  
Cy5.5, PE-Cy5, PE-Cy5.5, PE-Cy7, PE-Texas Red, and APC-Cy7.

Other fluorophores include, *inter alia*, Alexa Fluor® 350, Alexa Fluor® 488,  
Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa  
Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc.,  
30 Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY  
R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY  
564/570, BODIPY 576/589, BODIPY 581/591, BODIPY TR, BODIPY 630/650,  
BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B,

Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA), and Cy2, Cy3, Cy3.5, Cy5, Cy5.5, Cy7, all of which are also useful for fluorescently labeling the antibodies of the present invention.

- 5 For secondary detection using labeled avidin, streptavidin, captavidin or neutravidin, the antibodies of the present invention can usefully be labeled with biotin.

When the antibodies of the present invention are used, *e.g.*, for western blotting applications, they can usefully be labeled with radioisotopes, such as  $^{33}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^3\text{H}$ , and  $^{125}\text{I}$ . As another example, when the antibodies of the present invention are used for  
10 radioimmunoassay, the label can usefully be  $^{228}\text{Th}$ ,  $^{227}\text{Ac}$ ,  $^{225}\text{Ac}$ ,  $^{223}\text{Ra}$ ,  $^{213}\text{Bi}$ ,  $^{212}\text{Pb}$ ,  $^{212}\text{Bi}$ ,  $^{211}\text{At}$ ,  $^{203}\text{Pb}$ ,  $^{194}\text{Os}$ ,  $^{188}\text{Re}$ ,  $^{186}\text{Re}$ ,  $^{153}\text{Sm}$ ,  $^{149}\text{Tb}$ ,  $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{111}\text{In}$ ,  $^{105}\text{Rh}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{97}\text{Ru}$ ,  $^{90}\text{Y}$ ,  $^{90}\text{Sr}$ ,  $^{88}\text{Y}$ ,  $^{72}\text{Se}$ ,  $^{67}\text{Cu}$ , or  $^{47}\text{Sc}$ .

As another example, when the antibodies of the present invention are to be used for *in vivo* diagnostic use, they can be rendered detectable by conjugation to MRI contrast  
15 agents, such as gadolinium diethylenetriaminepentaacetic acid (DTPA), Lauffer *et al.*, *Radiology* 207(2): 529-38 (1998), or by radioisotopic labeling.

As would be understood, use of the labels described above is not restricted to the application as for which they were mentioned.

The antibodies of the present invention, including fragments and derivatives  
20 thereof, can also be conjugated to toxins, in order to target the toxin's ablative action to cells that display and/or express the polypeptides of the present invention. Commonly, the antibody in such immunotoxins is conjugated to Pseudomonas exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin lethal factor, or ricin. See Hall (ed.), Immunotoxin Methods and Protocols (Methods in Molecular Biology, vol. 166), Humana Press (2000);  
25 and Frankel *et al.* (eds.), Clinical Applications of Immunotoxins, Springer-Verlag (1998).

The antibodies of the present invention can usefully be attached to a substrate, and it is, therefore, another aspect of the invention to provide antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or  
30 the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, attached to a substrate. Substrates can be porous or nonporous, planar or nonplanar. For example, the antibodies of the present invention

can usefully be conjugated to filtration media, such as NHS-activated Sepharose or CNBr-activated Sepharose for purposes of immunoaffinity chromatography. For example, the antibodies of the present invention can usefully be attached to paramagnetic microspheres, typically by biotin-streptavidin interaction, which microsphere can then be used for  
5 isolation of cells that express or display the polypeptides of the present invention. As another example, the antibodies of the present invention can usefully be attached to the surface of a microtiter plate for ELISA.

As noted above, the antibodies of the present invention can be produced in prokaryotic and eukaryotic cells. It is, therefore, another aspect of the present invention to  
10 provide cells that express the antibodies of the present invention, including hybridoma cells, B cells, plasma cells, and host cells recombinantly modified to express the antibodies of the present invention.

In yet a further aspect, the present invention provides aptamers evolved to bind specifically to one or more of the HSPs of the present invention or to polypeptides  
15 encoded by the HSNAs of the invention.

In sum, one of skill in the art, provided with the teachings of this invention, has available a variety of methods which may be used to alter the biological properties of the antibodies of this invention including methods which would increase or decrease the stability or half-life, immunogenicity, toxicity, affinity or yield of a given antibody  
20 molecule, or to alter it in any other way that may render it more suitable for a particular application.

#### Transgenic Animals and Cells

In another aspect, the invention provides transgenic cells and non-human organisms comprising nucleic acid molecules of the invention. In a preferred  
25 embodiment, the transgenic cells and non-human organisms comprise a nucleic acid molecule encoding a HSP. In a preferred embodiment, the HSP comprises an amino acid sequence selected from SEQ ID NO: 410-611, or a fragment, mutein, homologous protein or allelic variant thereof. In another preferred embodiment, the transgenic cells and non-human organism comprise a HSNA of the invention, preferably a HSNA comprising a  
30 nucleotide sequence selected from the group consisting of SEQ ID NO: 1-409, or a part, substantially similar nucleic acid molecule, allelic variant or hybridizing nucleic acid molecule thereof.



In another embodiment, the transgenic cells and non-human organisms have a targeted disruption or replacement of the endogenous orthologue of the human HSG. The transgenic cells can be embryonic stem cells or somatic cells. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes.

5 Methods of producing transgenic animals are well known in the art. *See, e.g.*, Hogan *et al.*, Manipulating the Mouse Embryo: A Laboratory Manual, 2d ed., Cold Spring Harbor Press (1999); Jackson *et al.*, Mouse Genetics and Transgenics: A Practical Approach, Oxford University Press (2000); and Pinkert, Transgenic Animal Technology: A Laboratory Handbook, Academic Press (1999).

10 Any technique known in the art may be used to introduce a nucleic acid molecule of the invention into an animal to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection. (*see, e.g.*, Paterson *et al.*, *Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver *et al.*, *Biotechnology* 11: 1263-1270 (1993); Wright *et al.*, *Biotechnology* 9: 830-834 (1991); and U.S. Patent No.  
15 4,873,191, herein incorporated by reference in its entirety); retrovirus-mediated gene transfer into germ lines, blastocysts or embryos (*see, e.g.*, Van der Putten *et al.*, *Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)); gene targeting in embryonic stem cells (*see, e.g.*, Thompson *et al.*, *Cell* 56: 313-321 (1989)); electroporation of cells or embryos (*see, e.g.*, Lo, 1983, *Mol. Cell. Biol.* 3: 1803-1814 (1983)); introduction using a gene gun (*see, e.g.*, Ulmer *et al.*, *Science* 259: 1745-49 (1993); introducing nucleic acid constructs into  
20 embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (*see, e.g.*, Lavitrano *et al.*, *Cell* 57: 717-723 (1989)).

Other techniques include, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (*see, e.g.*,  
25 Campbell *et al.*, *Nature* 380: 64-66 (1996); Wilmut *et al.*, *Nature* 385: 810-813 (1997)). The present invention provides for transgenic animals that carry the transgene (*i.e.*, a nucleic acid molecule of the invention) in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.* *e.*, mosaic animals or chimeric animals.

The transgene may be integrated as a single transgene or as multiple copies, such  
30 as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, *e.g.*, the teaching of Lasko *et al. et al.*, *Proc. Natl. Acad. Sci. USA* 89: 6232- 6236 (1992).

The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished  
5 by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (RT-PCR).  
10 Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding  
15 strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to  
20 both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited  
25 to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Methods for creating a transgenic animal with a disruption of a targeted gene are  
30 also well known in the art. In general, a vector is designed to comprise some nucleotide sequences homologous to the endogenous targeted gene. The vector is introduced into a cell so that it may integrate, via homologous recombination with chromosomal sequences, into the endogenous gene, thereby disrupting the function of the endogenous gene. The

transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type. *See, e.g., Gu et al., Science* 265: 103-106 (1994). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. *See, e.g., Smithies et al., Nature* 317: 230-234 (1985); Thomas *et al., Cell* 51: 503-512 (1987); Thompson *et al., Cell* 5: 313-321 (1989).

In one embodiment, a mutant, non-functional nucleic acid molecule of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous nucleic acid sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene. *See, e.g., Thomas, supra* and Thompson, *supra*. However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g., knockouts*) are administered to a patient *in vivo*. Such cells may be obtained from an animal or patient or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g., lymphocytes*), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g., by transduction* (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. *See, e.g.*, U.S. Patent Nos. 5,399,349 and 5,460,959, each of which is incorporated by reference herein in its entirety.

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### Computer Readable Means

A further aspect of the invention is a computer readable means for storing the nucleic acid and amino acid sequences of the instant invention. In a preferred embodiment, the invention provides a computer readable means for storing SEQ ID NO: 410-611 and SEQ ID NO: 1-409 as described herein, as the complete set of sequences or in any combination. The records of the computer readable means can be accessed for reading and display and for interface with a computer system for the application of programs allowing for the location of data upon a query for data meeting certain criteria, the comparison of sequences, the alignment or ordering of sequences meeting a set of criteria, and the like.

The nucleic acid and amino acid sequences of the invention are particularly useful as components in databases useful for search analyses as well as in sequence analysis algorithms. As used herein, the terms "nucleic acid sequences of the invention" and "amino acid sequences of the invention" mean any detectable chemical or physical  
5 characteristic of a polynucleotide or polypeptide of the invention that is or may be reduced to or stored in a computer readable form. These include, without limitation, chromatographic scan data or peak data, photographic data or scan data therefrom, and mass spectrographic data.

This invention provides computer readable media having stored thereon sequences  
10 of the invention. A computer readable medium may comprise one or more of the following: a nucleic acid sequence comprising a sequence of a nucleic acid sequence of the invention; an amino acid sequence comprising an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences  
15 wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of one or more nucleic acid sequences of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said  
20 sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of a nucleic acid sequence of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the  
25 sequence of an amino acid sequence of the invention. The computer readable medium can be any composition of matter used to store information or data, including, for example, commercially available floppy disks, tapes, hard drives, compact disks, and video disks.

Also provided by the invention are methods for the analysis of character sequences, particularly genetic sequences. Preferred methods of sequence analysis  
30 include, for example, methods of sequence homology analysis, such as identity and similarity analysis, RNA structure analysis, sequence assembly, cladistic analysis, sequence motif analysis, open reading frame determination, nucleic acid base calling, and sequencing chromatogram peak analysis.

A computer-based method is provided for performing nucleic acid sequence identity or similarity identification. This method comprises the steps of providing a nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and comparing said nucleic acid sequence to at least one  
5 nucleic acid or amino acid sequence to identify sequence identity or similarity.

A computer-based method is also provided for performing amino acid homology identification, said method comprising the steps of: providing an amino acid sequence comprising the sequence of an amino acid of the invention in a computer readable medium; and comparing said amino acid sequence to at least one nucleic acid or an amino  
10 acid sequence to identify homology.

A computer-based method is still further provided for assembly of overlapping nucleic acid sequences into a single nucleic acid sequence, said method comprising the steps of: providing a first nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and screening for at least one  
15 overlapping region between said first nucleic acid sequence and a second nucleic acid sequence. In addition, the invention includes a method of using patterns of expression associated with either the nucleic acids or proteins in a computer-based method to diagnose disease.

#### Diagnostic Methods for hepatic Cancer

20 The present invention also relates to quantitative and qualitative diagnostic assays and methods for detecting, diagnosing, monitoring, staging and predicting cancers by comparing expression of a HSNA or a HSP in a human patient that has or may have hepatic cancer, or who is at risk of developing hepatic cancer, with the expression of a HSNA or a HSP in a normal human control. For purposes of the present invention,  
25 “expression of a HSNA” or “HSNA expression” means the quantity of HSNA mRNA that can be measured by any method known in the art or the level of transcription that can be measured by any method known in the art in a cell, tissue, organ or whole patient. Similarly, the term “expression of a HSP” or “HSP expression” means the amount of HSP that can be measured by any method known in the art or the level of translation of a  
30 HSNA that can be measured by any method known in the art.

The present invention provides methods for diagnosing hepatic cancer in a patient, by analyzing for changes in levels of HSNA or HSP in cells, tissues, organs or bodily

fluids compared with levels of HSNA or HSP in cells, tissues, organs or bodily fluids of preferably the same type from a normal human control, wherein an increase, or decrease in certain cases, in levels of a HSNA or HSP in the patient versus the normal human control is associated with the presence of hepatic cancer or with a predilection to the disease. In  
5 another preferred embodiment, the present invention provides methods for diagnosing hepatic cancer in a patient by analyzing changes in the structure of the mRNA of a HSG compared to the mRNA from a normal control. These changes include, without limitation, aberrant splicing, alterations in polyadenylation and/or alterations in 5' nucleotide capping. In yet another preferred embodiment, the present invention provides methods for  
10 diagnosing hepatic cancer in a patient by analyzing changes in a HSP compared to a HSP from a normal patient. These changes include, *e.g.*, alterations, including post translational modifications such as glycosylation and/or phosphorylation of the HSP or changes in the subcellular HSP localization.

For purposes of the present invention, diagnosing means that HSNA or HSP levels  
15 are used to determine the presence or absence of disease in a patient. As will be understood by those of skill in the art, measurement of other diagnostic parameters may be required for definitive diagnosis or determination of the appropriate treatment for the disease. The determination may be made by a clinician, a doctor, a testing laboratory, or a patient using an over the counter test. The patient may have symptoms of disease or may  
20 be asymptomatic. In addition, the HSNA or HSP levels of the present invention may be used as screening marker to determine whether further tests or biopsies are warranted. In addition, the HSNA or HSP levels may be used to determine the vulnerability or susceptibility to disease.

In a preferred embodiment, the expression of a HSNA is measured by determining  
25 the amount of a mRNA that encodes an amino acid sequence selected from SEQ ID NO: 410-611, a homolog, an allelic variant, or a fragment thereof. In a more preferred embodiment, the HSNA expression that is measured is the level of expression of a HSNA mRNA selected from SEQ ID NO: 1-409, or a hybridizing nucleic acid, homologous nucleic acid or allelic variant thereof, or a part of any of these nucleic acid molecules.  
30 HSNA expression may be measured by any method known in the art, such as those described *supra*, including measuring mRNA expression by Northern blot, quantitative or qualitative reverse transcriptase PCR (RT-PCR), microarray, dot or slot blots or *in situ* hybridization. *See, e.g.*, Ausubel (1992), *supra*; Ausubel (1999), *supra*; Sambrook

(1989), *supra*; and Sambrook (2001), *supra*. HSNA transcription may be measured by any method known in the art including using a reporter gene hooked up to the promoter of a HSG of interest or doing nuclear run-off assays. Alterations in mRNA structure, *e.g.*, aberrant splicing variants, may be determined by any method known in the art, including, RT-PCR followed by sequencing or restriction analysis. As necessary, HSNA expression may be compared to a known control, such as normal hepatic nucleic acid, to detect a change in expression.

In another preferred embodiment, the expression of a HSP is measured by determining the level of a HSP having an amino acid sequence selected from the group consisting of SEQ ID NO: 410-611, a homolog, an allelic variant, or a fragment thereof. Such levels are preferably determined in at least one of cells, tissues, organs and/or bodily fluids, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for diagnosing over- or underexpression of a HSNA or HSP compared to normal control bodily fluids, cells, or tissue samples may be used to diagnose the presence of hepatic cancer. The expression level of a HSP may be determined by any method known in the art, such as those described *supra*. In a preferred embodiment, the HSP expression level may be determined by radioimmunoassays, competitive-binding assays, ELISA, Western blot, FACS, immunohistochemistry, immunoprecipitation, proteomic approaches: two-dimensional gel electrophoresis (2D electrophoresis) and non-gel-based approaches such as mass spectrometry or protein interaction profiling. *See, e.g.*, Harlow (1999), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. Alterations in the HSP structure may be determined by any method known in the art, including, *e.g.*, using antibodies that specifically recognize phosphoserine, phosphothreonine or phosphotyrosine residues, two-dimensional polyacrylamide gel electrophoresis (2D PAGE) and/or chemical analysis of amino acid residues of the protein. *Id.*

In a preferred embodiment, a radioimmunoassay (RIA) or an ELISA is used. An antibody specific to a HSP is prepared if one is not already available. In a preferred embodiment, the antibody is a monoclonal antibody. The anti-HSP antibody is bound to a solid support and any free protein binding sites on the solid support are blocked with a protein such as bovine serum albumin. A sample of interest is incubated with the antibody on the solid support under conditions in which the HSP will bind to the anti-HSP antibody. The sample is removed, the solid support is washed to remove unbound material, and an



anti-HSP antibody that is linked to a detectable reagent (a radioactive substance for RIA and an enzyme for ELISA) is added to the solid support and incubated under conditions in which binding of the HSP to the labeled antibody will occur. After binding, the unbound labeled antibody is removed by washing. For an ELISA, one or more substrates are added to produce a colored reaction product that is based upon the amount of an HSP in the sample. For an RIA, the solid support is counted for radioactive decay signals by any method known in the art. Quantitative results for both RIA and ELISA typically are obtained by reference to a standard curve.

Other methods to measure HSP levels are known in the art. For instance, a competition assay may be employed wherein an anti-HSP antibody is attached to a solid support and an allocated amount of a labeled HSP and a sample of interest are incubated with the solid support. The amount of labeled HSP attached to the solid support can be correlated to the quantity of a HSP in the sample.

Of the proteomic approaches, 2D PAGE is a well known technique. Isolation of individual proteins from a sample such as serum is accomplished using sequential separation of proteins by isoelectric point and molecular weight. Typically, polypeptides are first separated by isoelectric point (the first dimension) and then separated by size using an electric current (the second dimension). In general, the second dimension is perpendicular to the first dimension. Because no two proteins with different sequences are identical on the basis of both size and charge, the result of 2D PAGE is a roughly square gel in which each protein occupies a unique spot. Analysis of the spots with chemical or antibody probes, or subsequent protein microsequencing can reveal the relative abundance of a given protein and the identity of the proteins in the sample.

Expression levels of a HSNA can be determined by any method known in the art, including PCR and other nucleic acid methods, such as ligase chain reaction (LCR) and nucleic acid sequence based amplification (NASBA), can be used to detect malignant cells for diagnosis and monitoring of various malignancies. For example, reverse-transcriptase PCR (RT-PCR) is a powerful technique which can be used to detect the presence of a specific mRNA population in a complex mixture of thousands of other mRNA species. In RT-PCR, an mRNA species is first reverse transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase; the cDNA is then amplified as in a standard PCR reaction.

Hybridization to specific DNA molecules (*e.g.*, oligonucleotides) arrayed on a solid support can be used to both detect the expression of and quantitate the level of expression of one or more HSNAs of interest. In this approach, all or a portion of one or more HSNAs is fixed to a substrate. A sample of interest, which may comprise RNA, *e.g.*,  
5 total RNA or polyA-selected mRNA, or a complementary DNA (cDNA) copy of the RNA is incubated with the solid support under conditions in which hybridization will occur between the DNA on the solid support and the nucleic acid molecules in the sample of interest. Hybridization between the substrate-bound DNA and the nucleic acid molecules in the sample can be detected and quantitated by several means, including, without  
10 limitation, radioactive labeling or fluorescent labeling of the nucleic acid molecule or a secondary molecule designed to detect the hybrid.

The above tests can be carried out on samples derived from a variety of cells, bodily fluids and/or tissue extracts such as homogenates or solubilized tissue obtained from a patient. Tissue extracts are obtained routinely from tissue biopsy and autopsy  
15 material. Bodily fluids useful in the present invention include blood, urine, saliva or any other bodily secretion or derivative thereof. As used herein "blood" includes whole blood, plasma, serum, circulating epithelial cells, constituents, or any derivative of blood.

In addition to detection in bodily fluids, the proteins and nucleic acids of the invention are suitable to detection by cell capture technology. Whole cells may be  
20 captured by a variety of methods for example magnetic separation, U.S. Patent Nos. 5,200,084; 5,186,827; 5,108,933; 4,925,788, the disclosures of which are incorporated herein by reference in their entireties. Epithelial cells may be captured using such products as Dynabeads® or CELLection™ (DynaL Biotech, Oslo, Norway). Alternatively, fractions of blood may be captured, *e.g.*, the buffy coat fraction (50mm cells isolated from  
25 5ml of blood) containing epithelial cells. In addition, cancer cells may be captured using the techniques described in WO 00/47998, the disclosure of which is incorporated herein by reference in its entirety. Once the cells are captured or concentrated, the proteins or nucleic acids are detected by the means described in the subject application. Alternatively, nucleic acids may be captured directly from blood samples, see U.S. Patent Nos.  
30 6,156,504, 5,501,963; or WO 01/42504, the disclosures of which are incorporated herein by reference in their entireties.

In a preferred embodiment, the specimen tested for expression of HSNA or HSP includes without limitation hepatic tissue, hepatic cells grown in cell culture, blood,

serum, lymph node tissue, and lymphatic fluid. In another preferred embodiment, especially when metastasis of a primary hepatic cancer is known or suspected, specimens include, without limitation, tissues from brain, bone, bone marrow, liver, lungs, colon, and adrenal glands. In general, the tissues may be sampled by biopsy, including, without  
5 limitation, needle biopsy, *e.g.*, transthoracic needle aspiration, cervical mediastinoscopy, endoscopic lymph node biopsy, video-assisted thoracoscopy, exploratory thoracotomy, bone marrow biopsy and bone marrow aspiration.

All the methods of the present invention may optionally include determining the expression levels of one or more other cancer markers in addition to determining the  
10 expression level of a HSNA or HSP. In many cases, the use of another cancer marker will decrease the likelihood of false positives or false negatives. In one embodiment, the one or more other cancer markers include other HSNA or HSPs as disclosed herein. Other cancer markers useful in the present invention will depend on the cancer being tested and are known to those of skill in the art. In a preferred embodiment, at least one other cancer  
15 marker in addition to a particular HSNA or HSP is measured. In a more preferred embodiment, at least two other additional cancer markers are used. In an even more preferred embodiment, at least three, more preferably at least five, even more preferably at least ten additional cancer markers are used.

## 20 *Diagnosing*

In one aspect, the invention provides a method for determining the expression levels and/or structural alterations of one or more HSNA and/or HSP in a sample from a patient suspected of having hepatic cancer. In general, the method comprises the steps of obtaining the sample from the patient, determining the expression level or structural  
25 alterations of a HSNA and/or HSP and then ascertaining whether the patient has hepatic cancer from the expression level of the HSNA or HSP. In general, if high expression relative to a control of a HSNA or HSP is indicative of hepatic cancer, a diagnostic assay is considered positive if the level of expression of the HSNA or HSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably  
30 five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a HSNA or HSP is indicative of hepatic cancer, a diagnostic assay is considered positive if the level of expression of the HSNA or HSP is at

least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

The present invention also provides a method of determining whether hepatic cancer has metastasized in a patient. One may identify whether the hepatic cancer has metastasized by measuring the expression levels and/or structural alterations of one or more HSNA and/or HSPs in a variety of tissues. The presence of a HSNA or HSP in a certain tissue at levels higher than that of corresponding noncancerous tissue (*e.g.*, the same tissue from another individual) is indicative of metastasis if high level expression of a HSNA or HSP is associated with hepatic cancer. Similarly, the presence of a HSNA or HSP in a tissue at levels lower than that of corresponding noncancerous tissue is indicative of metastasis if low level expression of a HSNA or HSP is associated with hepatic cancer. Further, the presence of a structurally altered HSNA or HSP that is associated with hepatic cancer is also indicative of metastasis.

In general, if high expression relative to a control of a HSNA or HSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the HSNA or HSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a HSNA or HSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the HSNA or HSP is at least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control.

### *Staging*

The invention also provides a method of staging hepatic cancer in a human patient. The method comprises identifying a human patient having hepatic cancer and analyzing cells, tissues or bodily fluids from such human patient for expression levels and/or structural alterations of one or more HSNA or HSPs. First, one or more tumors from a

variety of patients are staged according to procedures well known in the art, and the expression levels of one or more HSNA or HSPs is determined for each stage to obtain a standard expression level for each HSNA and HSP. Then, the HSNA or HSP expression levels of the HSNA or HSP are determined in a biological sample from a patient whose stage of cancer is not known. The HSNA or HSP expression levels from the patient are then compared to the standard expression level. By comparing the expression level of the HSNA and HSPs from the patient to the standard expression levels, one may determine the stage of the tumor. The same procedure may be followed using structural alterations of a HSNA or HSP to determine the stage of a hepatic cancer.

#### 10        *Monitoring*

Further provided is a method of monitoring hepatic cancer in a human patient. One may monitor a human patient to determine whether there has been metastasis and, if there has been, when metastasis began to occur. One may also monitor a human patient to determine whether a preneoplastic lesion has become cancerous. One may also monitor a human patient to determine whether a therapy, *e.g.*, chemotherapy, radiotherapy or surgery, has decreased or eliminated the hepatic cancer. The monitoring may determine if there has been a reoccurrence and, if so, determine its nature. The method comprises identifying a human patient that one wants to monitor for hepatic cancer, periodically analyzing cells, tissues or bodily fluids from such human patient for expression levels of one or more HSNA or HSPs, and comparing the HSNA or HSP levels over time to those HSNA or HSP expression levels obtained previously. Patients may also be monitored by measuring one or more structural alterations in a HSNA or HSP that are associated with hepatic cancer.

If increased expression of a HSNA or HSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting an increase in the expression level of a HSNA or HSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. One having ordinary skill in the art would recognize that if this were the case, then a decreased expression level would be indicative of no metastasis, effective therapy or failure to progress to a neoplastic lesion. If decreased expression of a HSNA or HSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting a decrease in the expression level of a HSNA or HSP indicates that

the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. In a preferred embodiment, the levels of HSNAs or HSPs are determined from the same cell type, tissue or bodily fluid as prior patient samples. Monitoring a patient for onset of hepatic cancer metastasis is periodic and preferably is done on a quarterly basis, but may be done more or less frequently.

The methods described herein can further be utilized as prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with increased or decreased expression levels of a HSNA and/or HSP. The present invention provides a method in which a test sample is obtained from a human patient and one or more HSNAs and/or HSPs are detected. The presence of higher (or lower) HSNA or HSP levels as compared to normal human controls is diagnostic for the human patient being at risk for developing cancer, particularly hepatic cancer. The effectiveness of therapeutic agents to decrease (or increase) expression or activity of one or more HSNAs and/or HSPs of the invention can also be monitored by analyzing levels of expression of the HSNAs and/or HSPs in a human patient in clinical trials or in *in vitro* screening assays such as in human cells. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the human patient or cells, as the case may be, to the agent being tested.

#### *Detection of Genetic Lesions or Mutations*

The methods of the present invention can also be used to detect genetic lesions or mutations in a HSG, thereby determining if a human with the genetic lesion is susceptible to developing hepatic cancer or to determine what genetic lesions are responsible, or are partly responsible, for a person's existing hepatic cancer. Genetic lesions can be detected, for example, by ascertaining the existence of a deletion, insertion and/or substitution of one or more nucleotides from the HSGs of this invention, a chromosomal rearrangement of a HSG, an aberrant modification of a HSG (such as of the methylation pattern of the genomic DNA), or allelic loss of a HSG. Methods to detect such lesions in the HSG of this invention are known to those having ordinary skill in the art following the teachings of the specification.

#### Methods of Detecting Noncancerous hepatic Diseases

The present invention also provides methods for determining the expression levels and/or structural alterations of one or more HSNAs and/or HSPs in a sample from a

patient suspected of having or known to have a noncancerous hepatic disease. In general, the method comprises the steps of obtaining a sample from the patient, determining the expression level or structural alterations of a HSNA and/or HSP, comparing the expression level or structural alteration of the HSNA or HSP to a normal hepatic control, and then ascertaining whether the patient has a noncancerous hepatic disease. In general, if high expression relative to a control of a HSNA or HSP is indicative of a particular noncancerous hepatic disease, a diagnostic assay is considered positive if the level of expression of the HSNA or HSP is at least two times higher, and more preferably are at least five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a HSNA or HSP is indicative of a noncancerous hepatic disease, a diagnostic assay is considered positive if the level of expression of the HSNA or HSP is at least two times lower, more preferably are at least five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

One having ordinary skill in the art may determine whether a HSNA and/or HSP is associated with a particular noncancerous hepatic disease by obtaining hepatic tissue from a patient having a noncancerous hepatic disease of interest and determining which HSNAs and/or HSPs are expressed in the tissue at either a higher or a lower level than in normal hepatic tissue. In another embodiment, one may determine whether a HSNA or HSP exhibits structural alterations in a particular noncancerous hepatic disease state by obtaining hepatic tissue from a patient having a noncancerous hepatic disease of interest and determining the structural alterations in one or more HSNAs and/or HSPs relative to normal hepatic tissue.

#### Methods for Identifying hepatic Tissue

In another aspect, the invention provides methods for identifying hepatic tissue. These methods are particularly useful in, *e.g.*, forensic science, hepatic cell differentiation and development, and in tissue engineering.

In one embodiment, the invention provides a method for determining whether a sample is hepatic tissue or has hepatic tissue-like characteristics. The method comprises the steps of providing a sample suspected of comprising hepatic tissue or having hepatic

tissue-like characteristics, determining whether the sample expresses one or more HSNAs and/or HSPs, and, if the sample expresses one or more HSNAs and/or HSPs, concluding that the sample comprises hepatic tissue. In a preferred embodiment, the HSNA encodes a polypeptide having an amino acid sequence selected from SEQ ID NO: 410-611, or a  
5 homolog, allelic variant or fragment thereof. In a more preferred embodiment, the HSNA has a nucleotide sequence selected from SEQ ID NO: 1-409, or a hybridizing nucleic acid, an allelic variant or a part thereof. Determining whether a sample expresses a HSNA can be accomplished by any method known in the art. Preferred methods include hybridization to microarrays, Northern blot hybridization, and quantitative or qualitative  
10 RT-PCR. In another preferred embodiment, the method can be practiced by determining whether a HSP is expressed. Determining whether a sample expresses a HSP can be accomplished by any method known in the art. Preferred methods include Western blot, ELISA, RIA and 2D PAGE. In one embodiment, the HSP has an amino acid sequence selected from SEQ ID NO: 410-611, or a homolog, allelic variant or fragment thereof. In  
15 another preferred embodiment, the expression of at least two HSNAs and/or HSPs is determined. In a more preferred embodiment, the expression of at least three, more preferably four and even more preferably five HSNAs and/or HSPs are determined.

In one embodiment, the method can be used to determine whether an unknown tissue is hepatic tissue. This is particularly useful in forensic science, in which small,  
20 damaged pieces of tissues that are not identifiable by microscopic or other means are recovered from a crime or accident scene. In another embodiment, the method can be used to determine whether a tissue is differentiating or developing into hepatic tissue. This is important in monitoring the effects of the addition of various agents to cell or tissue culture, *e.g.*, in producing new hepatic tissue by tissue engineering. These agents  
25 include, *e.g.*, growth and differentiation factors, extracellular matrix proteins and culture medium. Other factors that may be measured for effects on tissue development and differentiation include gene transfer into the cells or tissues, alterations in pH, aqueous:air interface and various other culture conditions.

#### Methods for Producing and Modifying hepatic Tissue

30 In another aspect, the invention provides methods for producing engineered hepatic tissue or cells. In one embodiment, the method comprises the steps of providing cells, introducing a HSNA or a HSG into the cells, and growing the cells under conditions



in which they exhibit one or more properties of hepatic tissue cells. In a preferred embodiment, the cells are pluripotent. As is well known in the art, normal hepatic tissue comprises a large number of different cell types. Thus, in one embodiment, the engineered hepatic tissue or cells comprises one of these cell types. In another embodiment, the engineered hepatic tissue or cells comprises more than one hepatic cell type. Further, the culture conditions of the cells or tissue may require manipulation in order to achieve full differentiation and development of the hepatic cell tissue. Methods for manipulating culture conditions are well known in the art.

Nucleic acid molecules encoding one or more HSPs are introduced into cells, preferably pluripotent cells. In a preferred embodiment, the nucleic acid molecules encode HSPs having amino acid sequences selected from SEQ ID NO: 410-611, or homologous proteins, analogs, allelic variants or fragments thereof. In a more preferred embodiment, the nucleic acid molecules have a nucleotide sequence selected from SEQ ID NO: 1-409, or hybridizing nucleic acids, allelic variants or parts thereof. In another highly preferred embodiment, a HSG is introduced into the cells. Expression vectors and methods of introducing nucleic acid molecules into cells are well known in the art and are described in detail, *supra*.

Artificial hepatic tissue may be used to treat patients who have lost some or all of their hepatic function.

## 20 Pharmaceutical Compositions

In another aspect, the invention provides pharmaceutical compositions comprising the nucleic acid molecules, polypeptides, fusion proteins, antibodies, antibody derivatives, antibody fragments, agonists, antagonists, or inhibitors of the present invention. In a preferred embodiment, the pharmaceutical composition comprises a HSNA or part thereof. In a more preferred embodiment, the HSNA has a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-409, a nucleic acid that hybridizes thereto, an allelic variant thereof, or a nucleic acid that has substantial sequence identity thereto. In another preferred embodiment, the pharmaceutical composition comprises a HSP or fragment thereof. In a more preferred embodiment, the pharmaceutical composition comprises a HSP having an amino acid sequence that is selected from the group consisting of SEQ ID NO: 410-611, a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof. In another preferred

embodiment, the pharmaceutical composition comprises an anti-HSP antibody, preferably an antibody that specifically binds to a HSP having an amino acid that is selected from the group consisting of SEQ ID NO: 410-611, or an antibody that binds to a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or  
5 an analog or derivative thereof.

Such a composition typically contains from about 0.1 to 90% by weight of a therapeutic agent of the invention formulated in and/or with a pharmaceutically acceptable carrier or excipient.

Pharmaceutical formulation is a well-established art that is further described in  
10 Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20<sup>th</sup> ed., Lippincott, Williams & Wilkins (2000); Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7<sup>th</sup> ed., Lippincott Williams & Wilkins (1999); and Kibbe (ed.), Handbook of Pharmaceutical Excipients American Pharmaceutical Association, 3<sup>rd</sup> ed. (2000) and thus need not be described in detail herein.

15 Briefly, formulation of the pharmaceutical compositions of the present invention will depend upon the route chosen for administration. The pharmaceutical compositions utilized in this invention can be administered by various routes including both enteral and parenteral routes, including oral, intravenous, intramuscular, subcutaneous, inhalation, topical, sublingual, rectal, intra-arterial, intramedullary, intrathecal, intraventricular,  
20 transmucosal, transdermal, intranasal, intraperitoneal, intrapulmonary, and intrauterine.

Oral dosage forms can be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Solid formulations of the compositions for oral administration can contain suitable carriers or excipients, such as carbohydrate or protein fillers, such as sugars, including  
25 lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or microcrystalline cellulose; gums including arabic and tragacanth; proteins such as gelatin and collagen; inorganics, such as kaolin, calcium carbonate, dicalcium phosphate, sodium chloride; and other agents such as acacia and  
30 alginic acid.

Agents that facilitate disintegration and/or solubilization can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate, microcrystalline cellulose, cornstarch, sodium starch glycolate, and alginic acid.

Tablet binders that can be used include acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone™), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearates, stearic acid, silicone  
5 fluid, talc, waxes, oils, and colloidal silica.

Fillers, agents that facilitate disintegration and/or solubilization, tablet binders and lubricants, including the aforementioned, can be used singly or in combination.

Solid oral dosage forms need not be uniform throughout. For example, dragee  
10 cores can be used in conjunction with suitable coatings, such as concentrated sugar solutions, which can also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Oral dosage forms of the present invention include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or  
15 sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

20 Additionally, dyestuffs or pigments can be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, *i.e.*, dosage.

Liquid formulations of the pharmaceutical compositions for oral (enteral) administration are prepared in water or other aqueous vehicles and can contain various suspending agents such as methylcellulose, alginates, tragacanth, pectin, kelgin,  
25 carrageenan, acacia, polyvinylpyrrolidone, and polyvinyl alcohol. The liquid formulations can also include solutions, emulsions, syrups and elixirs containing, together with the active compound(s), wetting agents, sweeteners, and coloring and flavoring agents.

The pharmaceutical compositions of the present invention can also be formulated for parenteral administration. Formulations for parenteral administration can be in the  
30 form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions.

For intravenous injection, water soluble versions of the compounds of the present invention are formulated in, or if provided as a lyophilate, mixed with, a physiologically acceptable fluid vehicle, such as 5% dextrose ("D5"), physiologically buffered saline,

0.9% saline, Hanks' solution, or Ringer's solution. Intravenous formulations may include carriers, excipients or stabilizers including, without limitation, calcium, human serum albumin, citrate, acetate, calcium chloride, carbonate, and other salts.

Intramuscular preparations, *e.g.* a sterile formulation of a suitable soluble salt form  
5 of the compounds of the present invention, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution. Alternatively, a suitable insoluble form of the compound can be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, such as an ester of a long chain fatty acid (*e.g.*, ethyl oleate), fatty oils such as sesame oil,  
10 triglycerides, or liposomes.

Parenteral formulations of the compositions can contain various carriers such as vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like).

15 Aqueous injection suspensions can also contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Non-lipid polycationic amino polymers can also be used for delivery. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

20 Pharmaceutical compositions of the present invention can also be formulated to permit injectable, long-term, deposition. Injectable depot forms may be made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of  
25 other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in microemulsions that are compatible with body tissues.

The pharmaceutical compositions of the present invention can be administered topically. For topical use the compounds of the present invention can also be prepared in  
30 suitable forms to be applied to the skin, or mucus membranes of the nose and throat, and can take the form of lotions, creams, ointments, liquid sprays or inhalants, drops, tinctures, lozenges, or throat paints. Such topical formulations further can include chemical compounds such as dimethylsulfoxide (DMSO) to facilitate surface penetration of the

active ingredient. In other transdermal formulations, typically in patch-delivered formulations, the pharmaceutically active compound is formulated with one or more skin penetrants, such as 2-N-methyl-pyrrolidone (NMP) or Azone. A topical semi-solid ointment formulation typically contains a concentration of the active ingredient from  
5 about 1 to 20%, *e.g.*, 5 to 10%, in a carrier such as a pharmaceutical cream base.

For application to the eyes or ears, the compounds of the present invention can be presented in liquid or semi-liquid form formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

For rectal administration the compounds of the present invention can be  
10 administered in the form of suppositories admixed with conventional carriers such as cocoa butter, wax or other glyceride.

Inhalation formulations can also readily be formulated. For inhalation, various powder and liquid formulations can be prepared. For aerosol preparations, a sterile formulation of the compound or salt form of the compound may be used in inhalers, such  
15 as metered dose inhalers, and nebulizers. Aerosolized forms may be especially useful for treating respiratory disorders.

Alternatively, the compounds of the present invention can be in powder form for reconstitution in the appropriate pharmaceutically acceptable carrier at the time of delivery.

20 The pharmaceutically active compound in the pharmaceutical compositions of the present invention can be provided as the salt of a variety of acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

25 After pharmaceutical compositions have been prepared, they are packaged in an appropriate container and labeled for treatment of an indicated condition.

The active compound will be present in an amount effective to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

30 A "therapeutically effective dose" refers to that amount of active ingredient, for example HSP polypeptide, fusion protein, or fragments thereof, antibodies specific for HSP, agonists, antagonists or inhibitors of HSP, which ameliorates the signs or symptoms

of the disease or prevent progression thereof; as would be understood in the medical arts, cure, although desired, is not required.

The therapeutically effective dose of the pharmaceutical agents of the present invention can be estimated initially by *in vitro* tests, such as cell culture assays, followed  
5 by assay in model animals, usually mice, rats, rabbits, dogs, or pigs. The animal model can also be used to determine an initial preferred concentration range and route of administration.

For example, the ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population) can be determined in one  
10 or more cell culture or animal model systems. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as LD50/ED50. Pharmaceutical compositions that exhibit large therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies are used in formulating an initial dosage range for human use, and preferably provide a range of  
15 circulating concentrations that includes the ED50 with little or no toxicity. After administration, or between successive administrations, the circulating concentration of active agent varies within this range depending upon pharmacokinetic factors well known in the art, such as the dosage form employed, sensitivity of the patient, and the route of administration.

20 The exact dosage will be determined by the practitioner, in light of factors specific to the subject requiring treatment. Factors that can be taken into account by the practitioner include the severity of the disease state, general health of the subject, age, weight, gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting  
25 pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. Where the therapeutic agent is a protein or antibody of the present invention, the therapeutic protein or antibody  
30 agent typically is administered at a daily dosage of 0.01 mg to 30 mg/kg of body weight of the patient (*e.g.*, 1 mg/kg to 5 mg/kg). The pharmaceutical formulation can be administered in multiple doses per day, if desired, to achieve the total desired daily dose.

Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical formulation(s) of the present invention to the patient. The pharmaceutical compositions of the present invention can be administered alone, or in combination with other therapeutic agents or interventions.

#### 10 Therapeutic Methods

The present invention further provides methods of treating subjects having defects in a gene of the invention, *e.g.*, in expression, activity, distribution, localization, and/or solubility, which can manifest as a disorder of hepatic function. As used herein, "treating" includes all medically-acceptable types of therapeutic intervention, including palliation and prophylaxis (prevention) of disease. The term "treating" encompasses any improvement of a disease, including minor improvements. These methods are discussed below.

##### *Gene Therapy and Vaccines*

The isolated nucleic acids of the present invention can also be used to drive *in vivo* expression of the polypeptides of the present invention. *In vivo* expression can be driven from a vector, typically a viral vector, often a vector based upon a replication incompetent retrovirus, an adenovirus, or an adeno-associated virus (AAV), for the purpose of gene therapy. *In vivo* expression can also be driven from signals endogenous to the nucleic acid or from a vector, often a plasmid vector, such as pVAX1 (Invitrogen, Carlsbad, CA, USA), for purpose of "naked" nucleic acid vaccination, as further described in U.S. Patent Nos. 5,589,466; 5,679,647; 5,804,566; 5,830,877; 5,843,913; 5,880,104; 5,958,891; 5,985,847; 6,017,897; 6,110,898; 6,204,250, the disclosures of which are incorporated herein by reference in their entireties. For cancer therapy, it is preferred that the vector also be tumor-selective. *See, e.g.*, Doronin *et al.*, *J. Virol.* 75: 3314-24 (2001).

In another embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a nucleic acid molecule of the present invention is administered. The nucleic acid molecule can be

delivered in a vector that drives expression of a HSP, fusion protein, or fragment thereof, or without such vector. Nucleic acid compositions that can drive expression of a HSP are administered, for example, to complement a deficiency in the native HSP, or as DNA vaccines. Expression vectors derived from virus, replication deficient retroviruses, adenovirus, adeno-associated (AAV) virus, herpes virus, or vaccinia virus can be used as  
5 can plasmids. *See, e.g., Cid-Arregui, supra.* In a preferred embodiment, the nucleic acid molecule encodes a HSP having the amino acid sequence of SEQ ID NO: 410-611, or a fragment, fusion protein, allelic variant or homolog thereof.

In still other therapeutic methods of the present invention, pharmaceutical  
10 compositions comprising host cells that express a HSP, fusions, or fragments thereof can be administered. In such cases, the cells are typically autologous, so as to circumvent xenogeneic or allotypic rejection, and are administered to complement defects in HSP production or activity. In a preferred embodiment, the nucleic acid molecules in the cells encode a HSP having the amino acid sequence of SEQ ID NO: 410-611, or a fragment,  
15 fusion protein, allelic variant or homolog thereof.

#### *Antisense Administration*

Antisense nucleic acid compositions, or vectors that drive expression of a HSG antisense nucleic acid, are administered to downregulate transcription and/or translation of a HSG in circumstances in which excessive production, or production of aberrant protein,  
20 is the pathophysiologic basis of disease.

Antisense compositions useful in therapy can have a sequence that is complementary to coding or to noncoding regions of a HSG. For example, oligonucleotides derived from the transcription initiation site, *e.g.,* between positions -10 and +10 from the start site, are preferred.

25 Catalytic antisense compositions, such as ribozymes, that are capable of sequence-specific hybridization to HSG transcripts, are also useful in therapy. *See, e.g., Phylactou, Adv. Drug Deliv. Rev. 44(2-3): 97-108 (2000); Phylactou et al., Hum. Mol. Genet. 7(10): 1649-53 (1998); Rossi, Ciba Found. Symp. 209: 195-204 (1997); and Sigurdsson et al., Trends Biotechnol. 13(8): 286-9 (1995).*

30 Other nucleic acids useful in the therapeutic methods of the present invention are those that are capable of triplex helix formation in or near the HSG genomic locus. Such triplexing oligonucleotides are able to inhibit transcription. *See, e.g., Intody et al., Nucleic*



*Acids Res.* 28(21): 4283-90 (2000); and McGuffie *et al.*, *Cancer Res.* 60(14): 3790-9 (2000). Pharmaceutical compositions comprising such triplex forming oligos (TFOs) are administered in circumstances in which excessive production, or production of aberrant protein, is a pathophysiologic basis of disease.

5 In a preferred embodiment, the antisense molecule is derived from a nucleic acid molecule encoding a HSP, preferably a HSP comprising an amino acid sequence of SEQ ID NO: 410-611, or a fragment, allelic variant or homolog thereof. In a more preferred embodiment, the antisense molecule is derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-409, or a part, allelic variant, substantially similar  
10 or hybridizing nucleic acid thereof.

#### *Polypeptide Administration*

In one embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a HSP, a fusion protein, fragment, analog or derivative thereof is administered to a subject with a  
15 clinically-significant HSP defect.

Protein compositions are administered, for example, to complement a deficiency in native HSP. In other embodiments, protein compositions are administered as a vaccine to elicit a humoral and/or cellular immune response to HSP. The immune response can be used to modulate activity of HSP or, depending on the immunogen, to immunize against  
20 aberrant or aberrantly expressed forms, such as mutant or inappropriately expressed isoforms. In yet other embodiments, protein fusions having a toxic moiety are administered to ablate cells that aberrantly accumulate HSP.

In a preferred embodiment, the polypeptide administered is a HSP comprising an amino acid sequence of SEQ ID NO: 410-611, or a fusion protein, allelic variant,  
25 homolog, analog or derivative thereof. In a more preferred embodiment, the polypeptide is encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-409, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

#### *Antibody, Agonist and Antagonist Administration*

In another embodiment of the therapeutic methods of the present invention, a  
30 therapeutically effective amount of a pharmaceutical composition comprising an antibody (including fragment or derivative thereof) of the present invention is administered. As is well known, antibody compositions are administered, for example, to antagonize activity

of HSP, or to target therapeutic agents to sites of HSP presence and/or accumulation. In a preferred embodiment, the antibody specifically binds to a HSP comprising an amino acid sequence of SEQ ID NO: 410-611, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the antibody specifically binds to a  
5 HSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-409, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

The present invention also provides methods for identifying modulators which bind to a HSP or have a modulatory effect on the expression or activity of a HSP. Modulators which decrease the expression or activity of HSP (antagonists) are believed to  
10 be useful in treating hepatic cancer. Such screening assays are known to those of skill in the art and include, without limitation, cell-based assays and cell-free assays. Small molecules predicted via computer imaging to specifically bind to regions of a HSP can also be designed, synthesized and tested for use in the imaging and treatment of hepatic cancer. Further, libraries of molecules can be screened for potential anticancer agents by  
15 assessing the ability of the molecule to bind to the HSPs identified herein. Molecules identified in the library as being capable of binding to a HSP are key candidates for further evaluation for use in the treatment of hepatic cancer. In a preferred embodiment, these molecules will downregulate expression and/or activity of a HSP in cells.

In another embodiment of the therapeutic methods of the present invention, a  
20 pharmaceutical composition comprising a non-antibody antagonist of HSP is administered. Antagonists of HSP can be produced using methods generally known in the art. In particular, purified HSP can be used to screen libraries of pharmaceutical agents, often combinatorial libraries of small molecules, to identify those that specifically bind and antagonize at least one activity of a HSP.

25 In other embodiments a pharmaceutical composition comprising an agonist of a HSP is administered. Agonists can be identified using methods analogous to those used to identify antagonists.

In a preferred embodiment, the antagonist or agonist specifically binds to and antagonizes or agonizes, respectively, a HSP comprising an amino acid sequence of SEQ  
30 ID NO: 410-611, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the antagonist or agonist specifically binds to and antagonizes or agonizes, respectively, a HSP encoded by a nucleic acid molecule having a

nucleotide sequence of SEQ ID NO: 1-409, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

#### *Targeting hepatic Tissue*

5           The invention also provides a method in which a polypeptide of the invention, or an antibody thereto, is linked to a therapeutic agent such that it can be delivered to the hepatic or to specific cells in the hepatic. In a preferred embodiment, an anti-HSP antibody is linked to a therapeutic agent and is administered to a patient in need of such therapeutic agent. The therapeutic agent may be a toxin, if hepatic tissue needs to be  
10 selectively destroyed. This would be useful for targeting and killing hepatic cancer cells. In another embodiment, the therapeutic agent may be a growth or differentiation factor, which would be useful for promoting hepatic cell function.

          In another embodiment, an anti-HSP antibody may be linked to an imaging agent that can be detected using, *e.g.*, magnetic resonance imaging, CT or PET. This would be  
15 useful for determining and monitoring hepatic function, identifying hepatic cancer tumors, and identifying noncancerous hepatic diseases.

### **EXAMPLES**

#### **Example 1: Gene Expression analysis**

##### *Custom CLASP Experiment*

20           HSGs were identified by a systematic analysis of gene expression data in the LIFESEQ® Gold database available from Incyte Genomics Inc (Palo Alto, CA) using the data mining software package CLASP™ (Candidate Lead Automatic Search Program). CLASP™ is a set of algorithms that interrogate Incyte's database to identify genes that are both specific to particular tissue types as well as differentially expressed in tissues from  
25 patients with cancer. LifeSeq® Gold contains information about which genes are expressed in various tissues in the body and about the dynamics of expression in both normal and diseased states. CLASP™ first sorts the LifeSeq® Gold database into defined tissue types, such as breast, ovary and prostate. CLASP™ categorizes each tissue sample by disease state. Disease states include "healthy," "cancer," "associated with cancer,"  
30 "other disease" and "other." Categorizing the disease states improves our ability to identify tissue and cancer-specific molecular targets. CLASP™ then performs a

simultaneous parallel search for genes that are expressed both (1) selectively in the defined tissue type compared to other tissue types and (2) differentially in the "cancer" disease state compared to the other disease states affecting the same, or different, tissues. This sorting is accomplished by using mathematical and statistical filters that specify the  
5 minimum change in expression levels and the minimum frequency that the differential expression pattern must be observed across the tissue samples for the gene to be considered statistically significant. The CLASP™ algorithm quantifies the relative abundance of a particular gene in each tissue type and in each disease state.

To find the HSGs of this invention, the following specific CLASP™ profiles were  
10 utilized: tissue-specific expression (CLASP 1), detectable expression only in cancer tissue (CLASP 2), maximal expression in cancer (CLASP 4) and differential expression in cancer tissue (CLASP 5). cDNA libraries were divided into 60 unique tissue types (early versions of LifeSeq® had 48 tissue types). Genes or ESTs were grouped into "gene bins," where each bin is a cluster of sequences grouped together where they share a common  
15 contig. The expression level for each gene bin was calculated for each tissue type. Differential expression significance was calculated with rigorous statistical significant testing taking into account variations in sample size and relative gene abundance in different libraries and within each library (for the equations used to determine statistically significant expression see Audic and Claverie "The significance of digital gene expression  
20 profiles," Genome Res 7(10): 986-995 (1997), including Equation 1 on page 987 and Equation 2 on page 988, the contents of which are incorporated by reference). Differentially expressed tissue-specific genes were selected based on the percentage abundance level in the targeted tissue versus all the other tissues (tissue-specificity). The expression levels for each gene in libraries of normal tissues or non-tumor tissues from  
25 cancer patients were compared with the expression levels in tissue libraries associated with tumor or disease (cancer-specificity). The results were analyzed for statistical significance.

The selection of the target genes meeting the rigorous CLASP™ profile criteria were as follows:

- 30 (a) CLASP 1: tissue-specific expression: To qualify as a CLASP 1 candidate, a gene must exhibit statistically significant expression in the tissue of interest compared to all other tissues. Only if the gene exhibits such differential

expression with a 90% of confidence level is it selected as a CLASP 1 candidate.

- (b) CLASP 2: detectable expression only in cancer tissue: To qualify as a CLASP 2 candidate, a gene must exhibit detectable expression in tumor tissues and undetectable expression in libraries from normal individuals and libraries from normal tissue obtained from diseased patients. In addition, such a gene must also exhibit further specificity for the tumor tissues of interest.
- (c) CLASP 4: maximum differential expression in cancer: To qualify as a CLASP 4 candidate, the lead must exhibit be one of the top50 genes showing maximal differential expression in cancer tissues. In addition, such a gene must also exhibit further specificity for the tumor tissues of interest.
- (d) CLASP 5: differential expression in cancer tissue: To qualify as a CLASP 5 candidate, a gene must be differentially expressed in tumor libraries in the tissue of interest compared to normal libraries for all tissues. Only if the gene exhibits such differential expression with a 90% of confidence level is it selected as a CLASP 5 candidate.

The CLASP scores for SEQ ID NO: 1-409 are listed below:

Expression data is not presented for many specific splice variants, however at least one transcript for the splice variant family is supported by expression data shown in the table.

- Splice variants may share similar regions among various transcripts and therefore data for one variant may be relevant to another. This supporting data is available on request.

There are 2 values for each organ in the format 9 - 0.9999. The first represent the number of occurrences of the gene in the given organ. The 2nd number represents the percentage of the expression of the gene in the given organ.

DEX0374_1. nt.1	SEQID NO. 1	CLASP2	LIV .0048				
DEX0374_2. nt.1	SEQID NO. 3	CLASP2	LIV .0081				
DEX0374_3. nt.1	SEQID NO. 5	CLASP5 CLASP1	LIV .0057	BRN .0001	INS .0019		
DEX0374_4. nt.1	SEQID NO. 30	CLASP2	LIV .0081				
DEX0374_5. nt.1	SEQID NO. 32	CLASP2	LIV .0048				
DEX0374_6. nt.1	SEQID NO. 34	CLASP2	LIV .0081				
DEX0374_7.	SEQID	CLASP1	LIV	SKN	STO		

nt.1	NO. 51		.0032	.0015	.0021		
DEX0374_8. nt.1	SEQID NO. 53	CLASP2	LIV .0081				
DEX0374_8. nt.2	SEQID NO. 54	CLASP2	LIV .0081				
DEX0374_9. nt.1	SEQID NO. 56	CLASP2 CLASP1	LIV .0194	BRN .0001			
DEX0374_10 .nt.1	SEQID NO. 58	CLASP2 CLASP1	LIV .0194				
DEX0374_11 .nt.1	SEQID NO. 60	CLASP2	LIV .0081				
DEX0374_12 .nt.1	SEQID NO. 65	CLASP2	LIV .0137				
DEX0374_13 .nt.1	SEQID NO. 67	CLASP2	LIV .0048				
DEX0374_14 .nt.1	SEQID NO. 69	CLASP2	LIV .0129				
DEX0374_15 .nt.1	SEQID NO. 70	CLASP2	LIV .0048				
DEX0374_15 .nt.2	SEQID NO. 71	CLASP2	LIV .0048				
DEX0374_16 .nt.1	SEQID NO. 73	CLASP1	LIV .0032				
DEX0374_16 .nt.2	SEQID NO. 74	CLASP1	LIV .0032				
DEX0374_17 .nt.1	SEQID NO. 104	CLASP2	LIV .0081				
DEX0374_18 .nt.1	SEQID NO. 113	CLASP2	LIV .0081				
DEX0374_18 .nt.2	SEQID NO. 114	CLASP2	LIV .0081				
DEX0374_19 .nt.1	SEQID NO. 117	CLASP2	LIV .0081				
DEX0374_20 .nt.1	SEQID NO. 119	CLASP2	LIV .0137				
DEX0374_20 .nt.2	SEQID NO. 120	CLASP2	LIV .0137				
DEX0374_21 .nt.1	SEQID NO. 121	CLASP2	LIV .0081				

DEX0374_22 .nt.1	SEQID NO. 123	CLASP2	LIV .0048	LNG .0011			
DEX0374_22 .nt.2	SEQID NO. 124	CLASP2	LIV .0048	LNG .0011			
DEX0374_23 .nt.1	SEQID NO. 126	CLASP2	LIV .0048				
DEX0374_23 .nt.2	SEQID NO. 127	CLASP2	LIV .0048				
DEX0374_24 .nt.1	SEQID NO. 131	CLASP2	LIV .0081				
DEX0374_25 .nt.1	SEQID NO. 134	CLASP2	LIV .0129				
DEX0374_26 .nt.1	SEQID NO. 136	CLASP2 CLASP1	LIV .0072	FTS .0004	UNC .0011		
DEX0374_27 .nt.1	SEQID NO. 137	CLASP5 CLASP1	LIV .0057	LMN .0017			
DEX0374_28 .nt.1	SEQID NO. 139	CLASP1	LIV .0043	UNC .0011			
DEX0374_28 .nt.2	SEQID NO. 140	CLASP1	LIV .0043	UNC .0011			
DEX0374_29 .nt.1	SEQID NO. 142	CLASP2	LIV .0048				
DEX0374_29 .nt.2	SEQID NO. 143	CLASP2	LIV .0048				
DEX0374_30 .nt.1	SEQID NO. 145	CLASP5 CLASP1	LIV .0057	BLO .0003	PRO .0003	FTS .0004	INL .0004
DEX0374_31 .nt.1	SEQID NO. 147	CLASP2	LIV .0081				
DEX0374_31 .nt.2	SEQID NO. 148	CLASP2	LIV .0081				
DEX0374_32 .nt.1	SEQID NO. 150	CLASP2	LIV .0048				
DEX0374_33 .nt.1	SEQID NO. 152	CLASP5 CLASP1	LIV .0057	MAM .0008			
DEX0374_34 .nt.1	SEQID NO. 154	CLASP2	LIV .0048				
DEX0374_35 .nt.1	SEQID NO. 157	CLASP2	LIV .0081				
DEX0374_36 .nt.1	SEQID NO.	CLASP1	LIV .0032				

	159						
DEX0374_37 .nt.1	SEQID NO. 162	CLASP2	LIV .0048				
DEX0374_38 .nt.1	SEQID NO. 164	CLASP2	LIV .0081	INL .0027			
DEX0374_38 .nt.2	SEQID NO. 165	CLASP2	LIV .0081	INL .0027			
DEX0374_39 .nt.1	SEQID NO. 167	CLASP1	LIV .0065				
DEX0374_39 .nt.2	SEQID NO. 168	CLASP1	LIV .0065				
DEX0374_40 .nt.1	SEQID NO. 170	CLASP2	LIV .0081				
DEX0374_41 .nt.1	SEQID NO. 172	CLASP2 CLASP1	LIV .0072	FTS .0004	UNC .0011		
DEX0374_42 .nt.1	SEQID NO. 174	CLASP2	LIV .0048				
DEX0374_43 .nt.1	SEQID NO. 176	CLASP2	LIV .0081				
DEX0374_43 .nt.2	SEQID NO. 177	CLASP2	LIV .0081				
DEX0374_44 .nt.1	SEQID NO. 180	CLASP1	LIV .0032				
DEX0374_45 .nt.1	SEQID NO. 182	CLASP2	LIV .0081				
DEX0374_46 .nt.1	SEQID NO. 184	CLASP2	LIV .0081	BRN .0021			
DEX0374_47 .nt.1	SEQID NO. 186	CLASP2 CLASP1	LIV .0122	THR .002	BMR .0029		
DEX0374_47 .nt.2	SEQID NO. 187	CLASP2 CLASP1	LIV .0122	THR .002	BMR .0029		
DEX0374_47 .nt.3	SEQID NO. 188	CLASP2 CLASP1	LIV .0122	THR .002	BMR .0029		
DEX0374_48 .nt.1	SEQID NO. 191	CLASP2	LIV .0081				
DEX0374_48 .nt.2	SEQID NO. 192	CLASP2	LIV .0081				
DEX0374_49 .nt.1	SEQID NO. 194	CLASP2	LIV .0048				
DEX0374_50	SEQID	CLASP5	LIV				



.nt.1	NO. 196	CLASP1	.0057				
DEX0374_51 .nt.1	SEQID NO. 198	CLASP2	LIV .0048				
DEX0374_52 .nt.1	SEQID NO. 201	CLASP2	LIV .0081				
DEX0374_53 .nt.1	SEQID NO. 203	CLASP2 CLASP1	LIV .0122	BRN .0001	FTS .0001		
DEX0374_53 .nt.2	SEQID NO. 204	CLASP2 CLASP1	LIV .0122	BRN .0001	FTS .0001		
DEX0374_54 .nt.1	SEQID NO. 229	CLASP2 CLASP1	LIV .0144	FTS .0001			
DEX0374_55 .nt.1	SEQID NO. 231	CLASP2	LIV .0081	ADR .0034			
DEX0374_56 .nt.1	SEQID NO. 233	CLASP2	LIV .0081				
DEX0374_56 .nt.2	SEQID NO. 234	CLASP2	LIV .0081				
DEX0374_57 .nt.1	SEQID NO. 246	CLASP2	LIV .0048				
DEX0374_58 .nt.1	SEQID NO. 248	CLASP1	LIV .0032	FTS .0001			
DEX0374_59 .nt.1	SEQID NO. 250	CLASP2	LIV .0081	URE .0078			
DEX0374_60 .nt.1	SEQID NO. 252	CLASP5 CLASP1	LIV .0132	INL .0004	FTS .0007	KID .0012	KID .0026
DEX0374_60 .nt.2	SEQID NO. 253	CLASP5 CLASP1	LIV .0132	INL .0004	FTS .0007	KID .0012	KID .0026
DEX0374_61 .nt.1	SEQID NO. 255	CLASP5 CLASP1	LIV .0057	MAM .0008			
DEX0374_62 .nt.1	SEQID NO. 257	CLASP2	LIV .0129				
DEX0374_63 .nt.1	SEQID NO. 259	CLASP1	LIV .0032	FTS .0001	UTR .0004		
DEX0374_63 .nt.2	SEQID NO. 260	CLASP1	LIV .0032	FTS .0001	UTR .0004		
DEX0374_64 .nt.1	SEQID NO. 262	CLASP2	LIV .0081				
DEX0374_64 .nt.2	SEQID NO. 263	CLASP2	LIV .0081				

DEX0374_65 .nt.1	SEQID NO. 265	CLASP1	LIV .0032	BRN .0003	FTS .0005		
DEX0374_65 .nt.2	SEQID NO. 266	CLASP1	LIV .0032	BRN .0003	FTS .0005		
DEX0374_66 .nt.1	SEQID NO. 268	CLASP2 CLASP1	LIV .0122	KID .0006	OVR .0007	GLB .0041	
DEX0374_67 .nt.1	SEQID NO. 270	CLASP2 CLASP1	LIV .0122	MAM .0004			
DEX0374_68 .nt.1	SEQID NO. 272	CLASP2	LIV .0048				
DEX0374_69 .nt.1	SEQID NO. 274	CLASP1	LIV .0032	FTS .0001	BRN .0004	INL .0008	UNC .0011
DEX0374_69 .nt.2	SEQID NO. 275	CLASP1	LIV .0032	FTS .0001	BRN .0004	INL .0008	UNC .0011
DEX0374_70 .nt.1	SEQID NO. 277	CLASP2	LIV .0081				
DEX0374_71 .nt.1	SEQID NO. 280	CLASP2	LIV .0081				
DEX0374_71 .nt.2	SEQID NO. 281	CLASP2	LIV .0081				
DEX0374_72 .nt.1	SEQID NO. 283	CLASP1	LIV .0032				
DEX0374_73 .nt.1	SEQID NO. 284	CLASP2	LIV .0129				
DEX0374_73 .nt.2	SEQID NO. 285	CLASP5		LMN .0028	LNG .0034	SPL .0063	UNC .016
DEX0374_74 .nt.1	SEQID NO. 297	CLASP2	LIV .0081	MAM .0019			
DEX0374_75 .nt.1	SEQID NO. 299	CLASP5 CLASP1	LIV .0094	FTS .0001	INL .0004	CRD .002	
DEX0374_76 .nt.1	SEQID NO. 301	CLASP2	LIV .0081				
DEX0374_76 .nt.2	SEQID NO. 302	CLASP2	LIV .0081				
DEX0374_77 .nt.1	SEQID NO. 303	CLASP2	LIV .0048				
DEX0374_78 .nt.1	SEQID NO. 305	CLASP2	LIV .0129				
DEX0374_79 .nt.1	SEQID NO.	CLASP2	LIV .0129	MAM .0009			

	307						
DEX0374_80 .nt.1	SEQID NO. 309	CLASP1	LIV .0032	FTS .0001			
DEX0374_81 .nt.1	SEQID NO. 329	CLASP1	LIV .0032				
DEX0374_82 .nt.1	SEQID NO. 331	CLASP5 CLASP1	LIV .013	FTS .0005	LMN .0034	ESO .0039	GLB .0041
DEX0374_82 .nt.2	SEQID NO. 332	CLASP5 CLASP1	LIV .013	FTS .0005	LMN .0034	ESO .0039	GLB .0041
DEX0374_82 .nt.3	SEQID NO. 333	CLASP5 CLASP1	LIV .013	FTS .0005	LMN .0034	ESO .0039	GLB .0041
DEX0374_82 .nt.4	SEQID NO. 334	CLASP5 CLASP1	LIV .013	FTS .0005	LMN .0034	ESO .0039	GLB .0041
DEX0374_82 .nt.5	SEQID NO. 335	CLASP5 CLASP1	LIV .013	FTS .0005	LMN .0034	ESO .0039	GLB .0041
DEX0374_83 .nt.1	SEQID NO. 341	CLASP2	LIV .0081	LNG .0014			
DEX0374_83 .nt.2	SEQID NO. 342	CLASP2	LIV .0081	LNG .0014			
DEX0374_84 .nt.1	SEQID NO. 344	CLASP2	LIV .0048				
DEX0374_85 .nt.1	SEQID NO. 346	CLASP2	LIV .0048				
DEX0374_86 .nt.1	SEQID NO. 379	CLASP1	LIV .0032	UNC .0011			
DEX0374_87 .nt.1	SEQID NO. 381	CLASP2	LIV .0081				
DEX0374_88 .nt.1	SEQID NO. 383	CLASP2	LIV .0081	NOS .0287			
DEX0374_88 .nt.2	SEQID NO. 384	CLASP5		PNS .0023	ESO .0102		
DEX0374_89 .nt.1	SEQID NO. 387	CLASP2	LIV .0129				
DEX0374_90 .nt.1	SEQID NO. 389	CLASP2	LIV .0048				
DEX0374_91 .nt.1	SEQID NO. 391	CLASP2	LIV .0048				
DEX0374_91 .nt.2	SEQID NO. 392	CLASP2	LIV .0048				
DEX0374_92	SEQID	CLASP2	LIV	LNG			

.nt.1	NO. 394		.0081	.001			
DEX0374_93 .nt.1	SEQID NO. 396	CLASP2	LIV .0048				
DEX0374_94 .nt.1	SEQID NO. 398	CLASP2	LIV .0065	OVR .0028			
DEX0374_95 .nt.1	SEQID NO. 400	CLASP2	LIV .0081	INL .0031			
DEX0374_96 .nt.1	SEQID NO. 402	CLASP2 CLASP1	LIV .0144	FTS .0001			
DEX0374_97 .nt.1	SEQID NO. 403	CLASP2 CLASP1	LIV .0144	FTS .0001			
DEX0374_98 .nt.1	SEQID NO. 404	CLASP5 CLASP1 CLASP4	LIV .0529	BRN .0003	BRN .0004	UTR .0004	UTR .0006
DEX0374_99 .nt.1	SEQID NO. 405	CLASP1	LIV .0032	SKN .0015	STO .0021		
DEX0374_10 0.nt.1	SEQID NO. 406	CLASP2	LIV .0081	CON .0016			
DEX0374_10 1.nt.1	SEQID NO. 407	CLASP5 CLASP3	LIV .0019	THY .002	PNS .0023	PAN .0024	TST .0027
DEX0374_10 2.nt.1	SEQID NO. 408	CLASP2	LIV .0129				
DEX0374_10 3.nt.1	SEQID NO. 409	CLASP2	LIV .0081				

## Abbreviation for tissues:

- 5 ADR Adrenal Glands, BLD Bladder, BLO Blood, BLV Blood Vessels, BRN Brain, CON Connective Tissue, ESO Esophagus, FTS Fetus, INL Intestine, Large, INS Intestine, Small, LNG Lung, MAM Breast, NRV Nervous Tissue, OVR Ovary, PAN Pancreas, PNS Penis, PRO Prostate, SPL Spleen, STO Stomach, SYN Synovial Membranes, THR Thyroid Gland, THY Thymus Gland, UNC Mixed Tissues, UTR Uterus

- 10 The mapping of the nucleic acid ("NT") SEQ ID NO; DEX ID; chromosomal location (if known); open reading frame (ORF) location; amino acid ("AA") SEQ ID NO and AA DEX ID are shown in the table below:

NT SEQ_No	NT_SEQID	Chromo Map	ORF_Loc	AA SEQ_NO	AA_SEQID
1	DEX0374_1.nt.1	13q14.11			
2	DEX0374_1.nt.2	13q14.11	-		
3	DEX0374_2.nt.1	*		410	DEX0374_2.aa.1
4	DEX0374_2.nt.2	*	-		
5	DEX0374_3.nt.1	7p14.1		411	DEX0374_3.aa.1
6	DEX0374_3.nt.2	7p14.1	29-2594	412	DEX0374_3.aa.2
7	DEX0374_3.nt.3	7p14.1	-		

8	DEX0374 3.nt.4	7p14.1	29-2594	412	DEX0374 3.aa.2
9	DEX0374 3.nt.5	7p14.1	29-2594	412	DEX0374 3.aa.2
10	DEX0374 3.nt.6	7p14.1	232-1410	413	DEX0374 3.aa.6
11	DEX0374 3.nt.7	7p14.1	-		
12	DEX0374 3.nt.8	7p14.1	-		
13	DEX0374 3.nt.9	7p14.1	29-2438	414	DEX0374 3.aa.9
14	DEX0374 3.nt.10	7p14.1	-		
15	DEX0374 3.nt.11	7p14.1	29-2594	412	DEX0374 3.aa.2
16	DEX0374 3.nt.12	7p14.1	29-2555	415	DEX0374 3.aa.12
17	DEX0374 3.nt.13	7p14.1	29-2358	416	DEX0374 3.aa.13
18	DEX0374 3.nt.14	7p14.1	29-1277	417	DEX0374 3.aa.14
19	DEX0374 3.nt.15	7p14.1	29-1070	418	DEX0374 3.aa.15
20	DEX0374 3.nt.16	7p14.1	29-506	419	DEX0374 3.aa.16
21	DEX0374 3.nt.17	7p14.1	-		
22	DEX0374 3.nt.18	7p14.1	29-2594	412	DEX0374 3.aa.2
23	DEX0374 3.nt.19	7p14.1	466-2805	420	DEX0374 3.aa.19
24	DEX0374 3.nt.20	7p14.1	29-2594	412	DEX0374 3.aa.2
25	DEX0374 3.nt.21	7p14.1	29-2594	412	DEX0374 3.aa.2
26	DEX0374 3.nt.22	7p14.1	29-2651	421	DEX0374 3.aa.22
27	DEX0374 3.nt.23	7p14.1	29-2510	422	DEX0374 3.aa.23
28	DEX0374 3.nt.24	7p14.1	29-1583	423	DEX0374 3.aa.24
29	DEX0374 3.nt.25	7p14.1	29-839	424	DEX0374 3.aa.25
30	DEX0374 4.nt.1	3p26.2		425	DEX0374 4.aa.1
31	DEX0374 4.nt.2	3p26.2	-		
32	DEX0374 5.nt.1	10q22.3		426	DEX0374 5.aa.1
33	DEX0374 5.nt.2	10q22.3	-		
34	DEX0374 6.nt.1	13q12.11			
35	DEX0374 6.nt.2	13q12.11	-		
36	DEX0374 6.nt.3	13q12.11	1-173	427	DEX0374 6.aa.3
37	DEX0374 6.nt.4	13q12.11	-		
38	DEX0374 6.nt.5	13q12.11	70-1023	428	DEX0374 6.aa.5
39	DEX0374 6.nt.6	13q12.11	-		
40	DEX0374 6.nt.7	13q12.11	-		
41	DEX0374 6.nt.8	13q12.11	-		
42	DEX0374 6.nt.9	13q12.11	-		
43	DEX0374 6.nt.10	13q12.11	70-1344	429	DEX0374 6.aa.10
44	DEX0374 6.nt.11	13q12.11	70-1053	430	DEX0374 6.aa.11
45	DEX0374 6.nt.12	13q12.11	70-681	431	DEX0374 6.aa.12
46	DEX0374 6.nt.13	13q12.11	-		
47	DEX0374 6.nt.14	13q12.11	-		
48	DEX0374 6.nt.15	13q12.11	1-533	432	DEX0374 6.aa.15
49	DEX0374 6.nt.16	13q12.11	70-1401	433	DEX0374 6.aa.16
50	DEX0374 6.nt.17	13q12.11	70-1218	434	DEX0374 6.aa.17
51	DEX0374 7.nt.1	1p32.2		435	DEX0374 7.aa.1
52	DEX0374 7.nt.2	1p32.2	-		
53	DEX0374 8.nt.1	3q29		436	DEX0374 8.aa.1
54	DEX0374 8.nt.2	3q29			
55	DEX0374 8.nt.3	3q29	-		
56	DEX0374 9.nt.1	1p32.3		437	DEX0374 9.aa.1
57	DEX0374 9.nt.2	1p32.3	-		
58	DEX0374 10.nt.1	7q33		438	DEX0374 10.aa.1
59	DEX0374 10.nt.2	7q33	-		
60	DEX0374 11.nt.1	5q12.3		439	DEX0374 11.aa.1
61	DEX0374 11.nt.2	5q12.3	-		
62	DEX0374 11.nt.3	5q12.3	-		
63	DEX0374 11.nt.4	5q12.3	-		
64	DEX0374 11.nt.5	5q12.3	-		

65	DEX0374 12.nt.1	3p22.1		440	DEX0374 12.aa.1
66	DEX0374 12.nt.2	3p22.1	-		
67	DEX0374 13.nt.1	6q14.1		441	DEX0374 13.aa.1
68	DEX0374 13.nt.2	6q14.1	-		
69	DEX0374 14.nt.1	14q22.2		442	DEX0374 14.aa.1
70	DEX0374 15.nt.1	1q24.3		443	DEX0374 15.aa.1
71	DEX0374 15.nt.2	1q24.3			
72	DEX0374 15.nt.3	1q24.3	-		
73	DEX0374 16.nt.1	14q13.2		444	DEX0374 16.aa.1
74	DEX0374 16.nt.2	14q13.2			
75	DEX0374 16.nt.3	*	-		
76	DEX0374 16.nt.4	*	73-2941	445	DEX0374 16.aa.4
77	DEX0374 16.nt.5	*	-		
78	DEX0374 16.nt.6	*	73-5737	446	DEX0374 16.aa.6
79	DEX0374 16.nt.7	*	513-4881	447	DEX0374 16.aa.7
80	DEX0374 16.nt.8	*	73-5389	448	DEX0374 16.aa.8
81	DEX0374 16.nt.9	*	16-4229	449	DEX0374 16.aa.9
82	DEX0374 16.nt.10	*	73-5737	446	DEX0374 16.aa.6
83	DEX0374 16.nt.11	*	73-5803	450	DEX0374 16.aa.11
84	DEX0374 16.nt.12	*	73-5737	446	DEX0374 16.aa.6
85	DEX0374 16.nt.13	*	-		
86	DEX0374 16.nt.14	*	-		
87	DEX0374 16.nt.15	*	73-5737	446	DEX0374 16.aa.6
88	DEX0374 16.nt.16	*	73-5186	451	DEX0374 16.aa.16
89	DEX0374 16.nt.17	*	73-3793	452	DEX0374 16.aa.17
90	DEX0374 16.nt.18	*	73-2623	453	DEX0374 16.aa.18
91	DEX0374 16.nt.19	*	-		
92	DEX0374 16.nt.20	*	73-928	454	DEX0374 16.aa.20
93	DEX0374 16.nt.21	*	73-1897	455	DEX0374 16.aa.21
94	DEX0374 16.nt.22	*	73-5878	456	DEX0374 16.aa.22
95	DEX0374 16.nt.23	*	572-4235	457	DEX0374 16.aa.23
96	DEX0374 16.nt.24	*	73-3454	458	DEX0374 16.aa.24
97	DEX0374 16.nt.25	*	73-5758	459	DEX0374 16.aa.25
98	DEX0374 16.nt.26	*	73-5677	460	DEX0374 16.aa.26
99	DEX0374 16.nt.27	*	73-5794	461	DEX0374 16.aa.27
100	DEX0374 16.nt.28	*	73-5743	462	DEX0374 16.aa.28
101	DEX0374 16.nt.29	*	73-2657	463	DEX0374 16.aa.29
102	DEX0374 16.nt.30	*	73-1366	464	DEX0374 16.aa.30
103	DEX0374 16.nt.31	*	73-1324	465	DEX0374 16.aa.31
104	DEX0374 17.nt.1	16q21		466	DEX0374 17.aa.1
105	DEX0374 17.nt.2	16q21	-		
106	DEX0374 17.nt.3	16q21	301-898	467	DEX0374 17.aa.3
107	DEX0374 17.nt.4	16q21	66-867	468	DEX0374 17.aa.4
108	DEX0374 17.nt.5	16q21	301-1054	469	DEX0374 17.aa.5
109	DEX0374 17.nt.6	16q21	43-310	470	DEX0374 17.aa.6
110	DEX0374 17.nt.7	16q21	301-823	471	DEX0374 17.aa.7
111	DEX0374 17.nt.8	16q21	301-823	471	DEX0374 17.aa.7
112	DEX0374 17.nt.9	16q21	392-725	472	DEX0374 17.aa.9
113	DEX0374 18.nt.1	14q32.32		473	DEX0374 18.aa.1
114	DEX0374 18.nt.2	14q32.32			
115	DEX0374 18.nt.3	14q32.32	-		
116	DEX0374 18.nt.4	*	-		
117	DEX0374 19.nt.1	14q32.32		474	DEX0374 19.aa.1
118	DEX0374 19.nt.2	14q32.32	-		
119	DEX0374 20.nt.1	2q31.1		475	DEX0374 20.aa.1
120	DEX0374 20.nt.2	2q31.1			
121	DEX0374 21.nt.1	10p12.33		476	DEX0374 21.aa.1

122	DEX0374 21.nt.2	10p12.33	-		
123	DEX0374 22.nt.1	11p13		477	DEX0374 22.aa.1
124	DEX0374 22.nt.2	11p13			
125	DEX0374 22.nt.3	11p13	-		
126	DEX0374 23.nt.1	1q31.3		478	DEX0374 23.aa.1
127	DEX0374 23.nt.2	1q31.3			
128	DEX0374 23.nt.3	1q31.3	-		
129	DEX0374 23.nt.4	1q31.3	-		
130	DEX0374 23.nt.5	1q31.3	-		
131	DEX0374 24.nt.1	16p13.3		479	DEX0374 24.aa.1
132	DEX0374 24.nt.2	16p13.3	629-1727	480	DEX0374 24.aa.2
133	DEX0374 24.nt.3	16p13.3	1215-2214	481	DEX0374 24.aa.3
134	DEX0374 25.nt.1	*		482	DEX0374 25.aa.1
135	DEX0374 25.nt.2	*	-		
136	DEX0374 26.nt.1	Xp11.23			
137	DEX0374 27.nt.1	16q24.3		483	DEX0374 27.aa.1
138	DEX0374 27.nt.2	16q24.3	1-199	484	DEX0374 27.aa.2
139	DEX0374 28.nt.1	10p12.1		485	DEX0374 28.aa.1
140	DEX0374 28.nt.2	10p12.1			
141	DEX0374 28.nt.3	10p12.1	-		
142	DEX0374 29.nt.1	2p13.1		486	DEX0374 29.aa.1
143	DEX0374 29.nt.2	2p13.1			
144	DEX0374 29.nt.3	2p13.1	-		
145	DEX0374 30.nt.1	1q23.3		487	DEX0374 30.aa.1
146	DEX0374 30.nt.2	1q23.3	-		
147	DEX0374 31.nt.1	1p34.3		488	DEX0374 31.aa.1
148	DEX0374 31.nt.2	1p34.3			
149	DEX0374 31.nt.3	1p34.3	-		
150	DEX0374 32.nt.1	Xp21.1		489	DEX0374 32.aa.1
151	DEX0374 32.nt.2	Xp21.1	-		
152	DEX0374 33.nt.1	1q31.3		490	DEX0374 33.aa.1
153	DEX0374 33.nt.2	1q31.3	-		
154	DEX0374 34.nt.1	6p22.2		491	DEX0374 34.aa.1
155	DEX0374 34.nt.2	6p22.2	-		
156	DEX0374 34.nt.3	6p22.2	-		
157	DEX0374 35.nt.1	16q13		492	DEX0374 35.aa.1
158	DEX0374 35.nt.2	16q13	75-546	493	DEX0374 35.aa.2
159	DEX0374 36.nt.1	12q23.3		494	DEX0374 36.aa.1
160	DEX0374 36.nt.2	12q23.3	-		
161	DEX0374 36.nt.3	*	-		
162	DEX0374 37.nt.1	18q12.3		495	DEX0374 37.aa.1
163	DEX0374 37.nt.2	18q12.3	-		
164	DEX0374 38.nt.1	17q21.31		496	DEX0374 38.aa.1
165	DEX0374 38.nt.2	17q21.31			
166	DEX0374 38.nt.3	17q21.31	-		
167	DEX0374 39.nt.1	20q11.23		497	DEX0374 39.aa.1
168	DEX0374 39.nt.2	20q11.23			
169	DEX0374 39.nt.3	20q11.23	1-134	498	DEX0374 39.aa.3
170	DEX0374 40.nt.1	14q23.3		499	DEX0374 40.aa.1
171	DEX0374 40.nt.2	14q23.3	-		
172	DEX0374 41.nt.1	*		500	DEX0374 41.aa.1
173	DEX0374 41.nt.2	*	-		
174	DEX0374 42.nt.1	14q23.3		501	DEX0374 42.aa.1
175	DEX0374 42.nt.2	14q23.3	-		
176	DEX0374 43.nt.1	*		502	DEX0374 43.aa.1
177	DEX0374 43.nt.2	*			

178	DEX0374 43.nt.3	*	179-560	503	DEX0374 43.aa.3
179	DEX0374 43.nt.4	*	-		
180	DEX0374 44.nt.1	16p12.3		504	DEX0374 44.aa.1
181	DEX0374 44.nt.2	16p12.3	-		
182	DEX0374 45.nt.1	5q31.1		505	DEX0374 45.aa.1
183	DEX0374 45.nt.2	5q31.1	157-583	506	DEX0374 45.aa.2
184	DEX0374 46.nt.1	*		507	DEX0374 46.aa.1
185	DEX0374 46.nt.2	*	-		
186	DEX0374 47.nt.1	6q25.1		508	DEX0374 47.aa.1
187	DEX0374 47.nt.2	6q25.1		509	DEX0374 47.aa.2
188	DEX0374 47.nt.3	6q25.1			
189	DEX0374 47.nt.4	6q25.1	-		
190	DEX0374 47.nt.5	6q25.1	-		
191	DEX0374 48.nt.1	*		510	DEX0374 48.aa.1
192	DEX0374 48.nt.2	*			
193	DEX0374 48.nt.3	*	-		
194	DEX0374 49.nt.1	18q12.3		511	DEX0374 49.aa.1
195	DEX0374 49.nt.2	18q12.3	-		
196	DEX0374 50.nt.1	20q11.23		512	DEX0374 50.aa.1
197	DEX0374 50.nt.2	20q11.23	-		
198	DEX0374 51.nt.1	2p23.3		513	DEX0374 51.aa.1
199	DEX0374 51.nt.2	2p23.3	-		
200	DEX0374 51.nt.3	2p23.3	-		
201	DEX0374 52.nt.1	13q12.11			
202	DEX0374 52.nt.2	13q12.11	-		
203	DEX0374 53.nt.1	*		514	DEX0374 53.aa.1
204	DEX0374 53.nt.2	*			
205	DEX0374 53.nt.3	16p11.2	82-2981	515	DEX0374 53.aa.3
206	DEX0374 53.nt.4	16p11.2	1-608	516	DEX0374 53.aa.4
207	DEX0374 53.nt.5	16p11.2	-		
208	DEX0374 53.nt.6	16p11.2	681-991	517	DEX0374 53.aa.6
209	DEX0374 53.nt.7	16p11.2	82-2958	518	DEX0374 53.aa.7
210	DEX0374 53.nt.8	16p11.2	82-2596	519	DEX0374 53.aa.8
211	DEX0374 53.nt.9	16p11.2	82-2596	519	DEX0374 53.aa.8
212	DEX0374 53.nt.10	16p11.2	91-1503	520	DEX0374 53.aa.10
213	DEX0374 53.nt.11	16p11.2	322-1079	521	DEX0374 53.aa.11
214	DEX0374 53.nt.12	16p11.2	82-2164	522	DEX0374 53.aa.12
215	DEX0374 53.nt.13	16p11.2	82-2176	523	DEX0374 53.aa.13
216	DEX0374 53.nt.14	16p11.2	133-889	524	DEX0374 53.aa.14
217	DEX0374 53.nt.15	16p11.2	82-1789	525	DEX0374 53.aa.15
218	DEX0374 53.nt.16	16p11.2	133-912	526	DEX0374 53.aa.16
219	DEX0374 53.nt.17	16p11.2	91-470	527	DEX0374 53.aa.17
220	DEX0374 53.nt.18	16p11.2	1-680	528	DEX0374 53.aa.18
221	DEX0374 53.nt.19	16p11.2	82-2836	529	DEX0374 53.aa.19
222	DEX0374 53.nt.20	16p11.2	82-2638	530	DEX0374 53.aa.20
223	DEX0374 53.nt.21	16p11.2	82-2861	531	DEX0374 53.aa.21
224	DEX0374 53.nt.22	16p11.2	82-3118	532	DEX0374 53.aa.22
225	DEX0374 53.nt.23	16p11.2	46-1018	533	DEX0374 53.aa.23
226	DEX0374 53.nt.24	16p11.2	1536-1844	517	DEX0374 53.aa.6
227	DEX0374 53.nt.25	*	196-1003	534	DEX0374 53.aa.25
228	DEX0374 53.nt.26	*	16-989	535	DEX0374 53.aa.26
229	DEX0374 54.nt.1	6q22.1		536	DEX0374 54.aa.1
230	DEX0374 54.nt.2	6q22.1	-		
231	DEX0374 55.nt.1	9q31.1		537	DEX0374 55.aa.1
232	DEX0374 55.nt.2	9q31.1	-		
233	DEX0374 56.nt.1	7q36.1		538	DEX0374 56.aa.1



234	DEX0374 56.nt.2	7q36.1			
235	DEX0374 56.nt.3	7q36.1	1-361	539	DEX0374 56.aa.3
236	DEX0374 56.nt.4	7q36.1	366-1980	540	DEX0374 56.aa.4
237	DEX0374 56.nt.5	7q36.1	335-1949	540	DEX0374 56.aa.4
238	DEX0374 56.nt.6	7q36.1	126-1740	540	DEX0374 56.aa.4
239	DEX0374 56.nt.7	7q36.1	126-1740	540	DEX0374 56.aa.4
240	DEX0374 56.nt.8	7q36.1	-		
241	DEX0374 56.nt.9	7q36.1	487-694	541	DEX0374 56.aa.9
242	DEX0374 56.nt.10	7q36.1	126-1740	540	DEX0374 56.aa.4
243	DEX0374 56.nt.11	7q36.1	487-2101	540	DEX0374 56.aa.4
244	DEX0374 56.nt.12	7q36.1	132-1785	542	DEX0374 56.aa.12
245	DEX0374 56.nt.13	7q36.1	126-723	543	DEX0374 56.aa.13
246	DEX0374 57.nt.1	6q22.1		544	DEX0374 57.aa.1
247	DEX0374 57.nt.2	6q22.1	-		
248	DEX0374 58.nt.1	13q34		545	DEX0374 58.aa.1
249	DEX0374 58.nt.2	13q34	-		
250	DEX0374 59.nt.1	3p14.1		546	DEX0374 59.aa.1
251	DEX0374 59.nt.2	3p14.1	-		
252	DEX0374 60.nt.1	10q11.23		547	DEX0374 60.aa.1
253	DEX0374 60.nt.2	10q11.23			
254	DEX0374 60.nt.3	10q11.23	22-371	548	DEX0374 60.aa.3
255	DEX0374 61.nt.1	1q31.3		549	DEX0374 61.aa.1
256	DEX0374 61.nt.2	1q31.3	-		
257	DEX0374 62.nt.1	17q25.3		550	DEX0374 62.aa.1
258	DEX0374 62.nt.2	17q25.3	-		
259	DEX0374 63.nt.1	1q25.1		551	DEX0374 63.aa.1
260	DEX0374 63.nt.2	1q25.1			
261	DEX0374 63.nt.3	1q25.1	-		
262	DEX0374 64.nt.1	14q12		552	DEX0374 64.aa.1
263	DEX0374 64.nt.2	14q12			
264	DEX0374 64.nt.3	14q12	-		
265	DEX0374 65.nt.1	16p12.1		553	DEX0374 65.aa.1
266	DEX0374 65.nt.2	16p12.1			
267	DEX0374 65.nt.3	16p12.1	-		
268	DEX0374 66.nt.1	16q13		554	DEX0374 66.aa.1
269	DEX0374 66.nt.2	16q13	-		
270	DEX0374 67.nt.1	19q13.31		555	DEX0374 67.aa.1
271	DEX0374 67.nt.2	19q13.31	-		
272	DEX0374 68.nt.1	3q29		556	DEX0374 68.aa.1
273	DEX0374 68.nt.2	3q29	-		
274	DEX0374 69.nt.1	8q12.3		557	DEX0374 69.aa.1
275	DEX0374 69.nt.2	8q12.3			
276	DEX0374 69.nt.3	8q12.3	-		
277	DEX0374 70.nt.1	5q33.1		558	DEX0374 70.aa.1
278	DEX0374 70.nt.2	5q33.1	1-180	559	DEX0374 70.aa.2
279	DEX0374 70.nt.3	5q33.1	1-168	560	DEX0374 70.aa.3
280	DEX0374 71.nt.1	16q13		561	DEX0374 71.aa.1
281	DEX0374 71.nt.2	16q13			
282	DEX0374 71.nt.3	16q13	-		
283	DEX0374 72.nt.1	6p21.1		562	DEX0374 72.aa.1
284	DEX0374 73.nt.1	12p13.33		563	DEX0374 73.aa.1
285	DEX0374 73.nt.2	12p13.33			
286	DEX0374 73.nt.3	12p13.33	1-966	564	DEX0374 73.aa.3
287	DEX0374 73.nt.4	12p13.33	1-966	564	DEX0374 73.aa.3
288	DEX0374 73.nt.5	12p13.33	1-966	564	DEX0374 73.aa.3
289	DEX0374 73.nt.6	12p13.33	1-966	564	DEX0374 73.aa.3
290	DEX0374 73.nt.7	12p13.33	1-966	564	DEX0374 73.aa.3

291	DEX0374 73.nt.8	12p13.33	737-1187	565	DEX0374 73.aa.8
292	DEX0374 73.nt.9	12p13.33	592-1756	566	DEX0374 73.aa.9
293	DEX0374 73.nt.10	12p13.33	-		
294	DEX0374 73.nt.11	12p13.33	1-97	567	DEX0374 73.aa.11
295	DEX0374 73.nt.12	12p13.33	592-1129	568	DEX0374 73.aa.12
296	DEX0374 73.nt.13	12p13.33	-		
297	DEX0374 74.nt.1	1q32.1		569	DEX0374 74.aa.1
298	DEX0374 74.nt.2	1q32.1	-		
299	DEX0374 75.nt.1	11q23.2			
300	DEX0374 75.nt.2	11q23.2	-		
301	DEX0374 76.nt.1	3q29		570	DEX0374 76.aa.1
302	DEX0374 76.nt.2	3q29			
303	DEX0374 77.nt.1	11q21		571	DEX0374 77.aa.1
304	DEX0374 77.nt.2	11q21	-		
305	DEX0374 78.nt.1	9p21.2		572	DEX0374 78.aa.1
306	DEX0374 78.nt.2	*	-		
307	DEX0374 79.nt.1	3q29		573	DEX0374 79.aa.1
308	DEX0374 79.nt.2	3q29	-		
309	DEX0374 80.nt.1	13q14.13		574	DEX0374 80.aa.1
310	DEX0374 80.nt.2	*	228-2415	575	DEX0374 80.aa.2
311	DEX0374 80.nt.3	*	-		
312	DEX0374 80.nt.4	*	-		
313	DEX0374 80.nt.5	*	228-2193	576	DEX0374 80.aa.5
314	DEX0374 80.nt.6	*	-		
315	DEX0374 80.nt.7	*	228-2319	577	DEX0374 80.aa.7
316	DEX0374 80.nt.8	*	31-209	578	DEX0374 80.aa.8
317	DEX0374 80.nt.9	*	-		
318	DEX0374 80.nt.10	*	1-198	579	DEX0374 80.aa.10
319	DEX0374 80.nt.11	*	228-2319	577	DEX0374 80.aa.7
320	DEX0374 80.nt.12	*	-		
321	DEX0374 80.nt.13	*	228-1839	580	DEX0374 80.aa.13
322	DEX0374 80.nt.14	*	228-1182	581	DEX0374 80.aa.14
323	DEX0374 80.nt.15	*	228-2319	577	DEX0374 80.aa.7
324	DEX0374 80.nt.16	*	73-612	582	DEX0374 80.aa.16
325	DEX0374 80.nt.17	*	228-2319	577	DEX0374 80.aa.7
326	DEX0374 80.nt.18	*	228-462	583	DEX0374 80.aa.18
327	DEX0374 80.nt.19	*	228-1737	584	DEX0374 80.aa.19
328	DEX0374 80.nt.20	*	228-684	585	DEX0374 80.aa.20
329	DEX0374 81.nt.1	8p11.21		586	DEX0374 81.aa.1
330	DEX0374 81.nt.2	8p11.21	-		
331	DEX0374 82.nt.1	*		587	DEX0374 82.aa.1
332	DEX0374 82.nt.2	*			
333	DEX0374 82.nt.3	*		588	DEX0374 82.aa.3
334	DEX0374 82.nt.4	*		589	DEX0374 82.aa.4
335	DEX0374 82.nt.5	*			
336	DEX0374 82.nt.6	*	1536-2034	590	DEX0374 82.aa.6
337	DEX0374 82.nt.7	*	37-606	591	DEX0374 82.aa.7
338	DEX0374 82.nt.8	*	37-606	591	DEX0374 82.aa.7
339	DEX0374 82.nt.9	*	109-370	592	DEX0374 82.aa.9
340	DEX0374 82.nt.10	*	37-606	591	DEX0374 82.aa.7
341	DEX0374 83.nt.1	1p34.1			
342	DEX0374 83.nt.2	1p34.1			
343	DEX0374 83.nt.3	1p34.1	-		
344	DEX0374 84.nt.1	2q21.3		593	DEX0374 84.aa.1
345	DEX0374 84.nt.2	2q21.3	-		
346	DEX0374 85.nt.1	8p11.21		594	DEX0374 85.aa.1

347	DEX0374 85.nt.2	8p11.21	-		
348	DEX0374 85.nt.3	8p11.21	-		
349	DEX0374 85.nt.4	8p11.21	-		
350	DEX0374 85.nt.5	8p11.21	139-424	595	DEX0374 85.aa.5
351	DEX0374 85.nt.6	8p11.21	121-405	596	DEX0374 85.aa.6
352	DEX0374 85.nt.7	8p11.21	-		
353	DEX0374 85.nt.8	8p11.21	-		
354	DEX0374 85.nt.9	8p11.21	-		
355	DEX0374 85.nt.10	8p11.21	-		
356	DEX0374 85.nt.11	8p11.21	1-249	597	DEX0374 85.aa.11
357	DEX0374 85.nt.12	8p11.21	-		
358	DEX0374 85.nt.13	8p11.21	-		
359	DEX0374 85.nt.14	8p11.21	-		
360	DEX0374 85.nt.15	8p11.21	-		
361	DEX0374 85.nt.16	8p11.21	-		
362	DEX0374 85.nt.17	8p11.21	-		
363	DEX0374 85.nt.18	8p11.21	-		
364	DEX0374 85.nt.19	8p11.21	-		
365	DEX0374 85.nt.20	8p11.21	1-436	598	DEX0374 85.aa.20
366	DEX0374 85.nt.21	8p11.21	1-436	598	DEX0374 85.aa.20
367	DEX0374 85.nt.22	8p11.21	1-436	598	DEX0374 85.aa.20
368	DEX0374 85.nt.23	8p11.21	1-436	598	DEX0374 85.aa.20
369	DEX0374 85.nt.24	8p11.21	-		
370	DEX0374 85.nt.25	8p11.21	-		
371	DEX0374 85.nt.26	8p11.21	1-436	598	DEX0374 85.aa.20
372	DEX0374 85.nt.27	8p11.21	-		
373	DEX0374 85.nt.28	8p11.21	1-436	598	DEX0374 85.aa.20
374	DEX0374 85.nt.29	8p11.21	1-436	598	DEX0374 85.aa.20
375	DEX0374 85.nt.30	8p11.21	1-436	598	DEX0374 85.aa.20
376	DEX0374 85.nt.31	8p11.21	1-436	598	DEX0374 85.aa.20
377	DEX0374 85.nt.32	8p11.21	1-436	598	DEX0374 85.aa.20
378	DEX0374 85.nt.33	8p11.21	-		
379	DEX0374 86.nt.1	11p15.5		599	DEX0374 86.aa.1
380	DEX0374 86.nt.2	11p15.5	88-471	600	DEX0374 86.aa.2
381	DEX0374 87.nt.1	3q25.1		601	DEX0374 87.aa.1
382	DEX0374 87.nt.2	3q25.1	-		
383	DEX0374 88.nt.1	1q42.2		602	DEX0374 88.aa.1
384	DEX0374 88.nt.2	1q42.2			
385	DEX0374 88.nt.3	1q42.2	254-659	603	DEX0374 88.aa.3
386	DEX0374 88.nt.4	1q42.2	-		
387	DEX0374 89.nt.1	1p32.1		604	DEX0374 89.aa.1
388	DEX0374 89.nt.2	1p32.1	-		
389	DEX0374 90.nt.1	15q25.1		605	DEX0374 90.aa.1
390	DEX0374 90.nt.2	15q25.1	-		
391	DEX0374 91.nt.1	1p21.3		606	DEX0374 91.aa.1
392	DEX0374 91.nt.2	1p21.3			
393	DEX0374 91.nt.3	1p21.3	-		
394	DEX0374 92.nt.1	13q33.1			
395	DEX0374 92.nt.2	13q33.1	-		
396	DEX0374 93.nt.1	5q14.1		607	DEX0374 93.aa.1
397	DEX0374 93.nt.2	5q14.1	-		
398	DEX0374 94.nt.1	2q35		608	DEX0374 94.aa.1
399	DEX0374 94.nt.2	2q35	-		
400	DEX0374 95.nt.1	2q35		609	DEX0374 95.aa.1
401	DEX0374 95.nt.2	2q35	1-417	610	DEX0374 95.aa.2
402	DEX0374 96.nt.1	6q22.1			
403	DEX0374 97.nt.1	6q22.1			

404	DEX0374 98.nt.1	12q23.3			
405	DEX0374 99.nt.1	1p32.2			
406	DEX0374 100.nt.1	9q31.3		611	DEX0374 100.aa.1
407	DEX0374 101.nt.1	2q11.2			
408	DEX0374 102.nt.1	7q22.1			
409	DEX0374 103.nt.1	*			

For the polypeptides of the invention, the following attributes were found, epitopes, post translational modifications, signal peptides and transmembrane domains.

- 5 Antigenicity (Epitope) prediction was performed through the antigenic module in the EMBOSS package. Rice, P., EMBOSS: The European Molecular Biology Open Software Suite, *Trends in Genetics* 16(6): 276-277 (2000). The antigenic module predicts potentially antigenic regions of a protein sequence, using the method of Kolaskar and Tongaonkar. Kolaskar, AS and Tongaonkar, PC., A semi-empirical method for prediction
- 10 of antigenic determinants on protein antigens, *FEBS Letters* 276: 172-174 (1990). Examples of post-translational modifications (PTMs) and other motifs of the HSPs of this invention are listed below. In addition, antibodies that specifically bind such post-translational modifications may be useful as a diagnostic or as therapeutic. The PTMs and other motifs were predicted by using the ProSite Dictionary of Proteins Sites and Patterns
- 15 (Bairoch *et al.*, *Nucleic Acids Res.* 25(1):217-221 (1997)), the following motifs, including PTMs, were predicted for the HSPs of the invention. The signal peptides were detected by using the SignalP 2.0, *see* Nielsen *et al.*, *Protein Engineering* 12, 3-9 (1999). Prediction of transmembrane helices in proteins was performed by the application TMHMM 2.0, “currently the best performing transmembrane prediction program”, according to authors
- 20 (Krogh *et al.*, *Journal of Molecular Biology*, 305(3):567-580, (2001); Moller *et al.*, *Bioinformatics*, 17(7):646-653, (2001); Sonnhammer, *et al.*, *A hidden Markov model for predicting transmembrane helices in protein sequences* in Glasgow, *et al.* Ed. Proceedings of the Sixth International Conference on Intelligent Systems for Molecular Biology, pages 175-182, Menlo Park, CA, 1998. AAI Press. The PSORT II program may also be used
- 25 to predict cellular localizations. Horton *et al.*, *Intelligent Systems for Molecular Biology* 5: 147-152 (1997). The table below includes the following sequence annotations: Signal peptide presence; TM (number of membrane domain, topology in orientation and position); Amino acid location and antigenic index (location, AI score, length); PTM and other motifs (type, amino acid residue locations).

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_3. aa.2	N	0 -o	268-290,1.26; 791-817,1.253; 237-246,1.216; 489-500,1.199; 44-73,1.187; 592- 604,1.181; 212- 233,1.172; 122- 146,1.171; 439- 471,1.17; 107- 114,1.165; 740- 774,1.16; 719- 729,1.16; 344- 358,1.159; 255- 265,1.137; 580- 586,1.135; 527- 551,1.132; 832- 840,1.132; 392- 408,1.127; 697- 712,1.12; 654- 661,1.12; 626- 651,1.117; 553- 561,1.117; 79- 90,1.113; 297- 317,1.107; 192- 198,1.104; 819- 825,1.1; 781- 788,1.094; 614- 623,1.093; 511- 520,1.092; 148- 155,1.082; 412- 421,1.08; 428- 436,1.079; 333- 339,1.074; 319- 325,1.071; 677- 686,1.066; 99- 105,1.066; 179- 185,1.057	Amidation 152-155; Asn_Glycosylation 80- 83, 232-235, 494-497, 512-515; Camp_Phospho_Site 507-510; Ck2_Phospho_Site 16- 19, 20-23, 24-27, 29- 32, 57-60, 96-99, 120- 123, 247-250, 268-271, 299-302, 318-321, 345- 348, 355-358, 476-479, 518-521, 556-559, 724- 727; Myristyl 66-71, 117-122, 177-182, 445- 450, 669-674, 717-722; Pkc_Phospho_Site 82- 84, 145-147, 181-183, 217-219, 242-244, 247- 249, 296-298, 299-301, 328-330, 355-357, 390- 392, 538-540, 556-558, 569-571, 584-586, 844- 846; Rgd 413-415, 456-458; Tyr_Phospho_Site 517- 525, 655-663;
DEX0374_3. aa.6	N	0 -o	329-355,1.253; 27-38,1.199; 130- 142,1.181; 278- 312,1.16; 257- 267,1.16; 118- 124,1.135; 65- 89,1.132; 370- 378,1.132; 235- 250,1.12; 192- 199,1.12; 164- 189,1.117; 91- 99,1.117; 357- 363,1.1; 319- 326,1.094; 152- 161,1.093; 49- 58,1.092; 215- 224,1.066	Asn_Glycosylation 32- 35, 50-53; Camp_Phospho_Site 45- 48; Ck2_Phospho_Site 14-17, 56-59, 94-97, 262-265; Myristyl 207-212, 255-260; Pkc_Phospho_Site 76- 78, 94-96, 107-109, 122-124, 382-384; Tyr_Phospho_Site 55- 63, 193-201;
	N	0 -o	268-290,1.26;	Amidation 152-155;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_3. aa.9			237-246,1.216; 489-500,1.199; 44-73,1.187; 592- 604,1.181; 212- 233,1.172; 791- 799,1.172; 122- 146,1.171; 439- 471,1.17; 107- 114,1.165; 740- 774,1.16; 719- 729,1.16; 344- 358,1.159; 255- 265,1.137; 580- 586,1.135; 527- 551,1.132; 392- 408,1.127; 697- 712,1.12; 654- 661,1.12; 626- 651,1.117; 553- 561,1.117; 79- 90,1.113; 297- 317,1.107; 192- 198,1.104; 781- 788,1.094; 614- 623,1.093; 511- 520,1.092; 148- 155,1.082; 412- 421,1.08; 428- 436,1.079; 333- 339,1.074; 319- 325,1.071; 677- 686,1.066; 99- 105,1.066; 179- 185,1.057	Asn_Glycosylation 80- 83, 232-235, 494-497, 512-515; Camp_Phospho_Site 507-510; Ck2_Phospho_Site 16- 19, 20-23, 24-27, 29- 32, 57-60, 96-99, 120- 123, 247-250, 268-271, 299-302, 318-321, 345- 348, 355-358, 476-479, 518-521, 556-559, 724- 727; Myristyl 66-71, 117-122, 177-182, 445- 450, 669-674, 717-722; Pkc_Phospho_Site 82- 84, 145-147, 181-183, 217-219, 242-244, 247- 249, 296-298, 299-301, 328-330, 355-357, 390- 392, 538-540, 556-558, 569-571, 584-586; Rgd 413-415, 456-458; Tyr_Phospho_Site 517- 525, 655-663;
DEX0374_3. aa.12	N	0 -o	268-290,1.26; 791-817,1.253; 237-246,1.216; 489-500,1.199; 44-73,1.187; 592- 604,1.181; 212- 233,1.172; 122- 146,1.171; 439- 471,1.17; 107- 114,1.165; 740- 774,1.16; 719- 729,1.16; 344- 358,1.159; 255- 265,1.137; 580- 586,1.135; 527- 551,1.132; 392- 408,1.127; 697- 712,1.12; 654- 661,1.12; 626- 651,1.117; 553- 561,1.117; 79-	Amidation 152-155; Asn_Glycosylation 80- 83, 232-235, 494-497, 512-515; Camp_Phospho_Site 507-510; Ck2_Phospho_Site 16- 19, 20-23, 24-27, 29- 32, 57-60, 96-99, 120- 123, 247-250, 268-271, 299-302, 318-321, 345- 348, 355-358, 476-479, 518-521, 556-559, 724- 727; Myristyl 66-71, 117-122, 177-182, 445- 450, 669-674, 717-722; Pkc_Phospho_Site 82- 84, 145-147, 181-183, 217-219, 242-244, 247- 249, 296-298, 299-301, 328-330, 355-357, 390-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			90,1.113; 297-317,1.107; 192-198,1.104; 819-836,1.1; 781-788,1.094; 614-623,1.093; 511-520,1.092; 148-155,1.082; 412-421,1.08; 428-436,1.079; 333-339,1.074; 319-325,1.071; 677-686,1.066; 99-105,1.066; 179-185,1.057	392, 538-540, 556-558, 569-571, 584-586; Rgd 413-415, 456-458; Tyr_Phospho_Site 517-525, 655-663;
DEX0374_3. aa.13	N	0 -o	268-290,1.26; 237-246,1.216; 489-500,1.199; 44-73,1.187; 592-604,1.181; 212-233,1.172; 122-146,1.171; 439-471,1.17; 107-114,1.165; 719-729,1.16; 344-358,1.159; 740-773,1.142; 255-265,1.137; 580-586,1.135; 527-551,1.132; 392-408,1.127; 697-712,1.12; 654-661,1.12; 626-651,1.117; 553-561,1.117; 79-90,1.113; 297-317,1.107; 192-198,1.104; 614-623,1.093; 511-520,1.092; 148-155,1.082; 412-421,1.08; 428-436,1.079; 333-339,1.074; 319-325,1.071; 677-686,1.066; 99-105,1.066; 179-185,1.057	Amidation 152-155; Asn_Glycosylation 80-83, 232-235, 494-497, 512-515; Camp_Phospho_Site 507-510; Ck2_Phospho_Site 16-19, 20-23, 24-27, 29-32, 57-60, 96-99, 120-123, 247-250, 268-271, 299-302, 318-321, 345-348, 355-358, 476-479, 518-521, 556-559, 724-727, 768-771; Myristyl 66-71, 117-122, 177-182, 445-450, 669-674, 717-722; Pkc_Phospho_Site 82-84, 145-147, 181-183, 217-219, 242-244, 247-249, 296-298, 299-301, 328-330, 355-357, 390-392, 538-540, 556-558, 569-571, 584-586; Rgd 413-415, 456-458; Tyr_Phospho_Site 517-525, 655-663;
DEX0374_3. aa.14	N	0 -o	268-290,1.26; 237-246,1.216; 44-73,1.187; 212-233,1.172; 122-146,1.171; 107-114,1.165; 344-358,1.159; 255-	Amidation 152-155; Asn_Glycosylation 80-83, 232-235; Camp_Phospho_Site 415-418; Ck2_Phospho_Site 16-19, 20-23, 24-27, 29-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			265,1.137; 79-90,1.113; 392-408,1.108; 297-317,1.107; 192-198,1.104; 148-155,1.082; 333-339,1.074; 319-325,1.071; 99-105,1.066; 179-185,1.057	32, 57-60, 96-99, 120-123, 247-250, 268-271, 299-302, 318-321, 345-348, 355-358; Myristyl 66-71, 117-122, 177-182; Pkc_Phospho_Site 82-84, 145-147, 181-183, 217-219, 242-244, 247-249, 296-298, 299-301, 328-330, 355-357, 390-392;
DEX0374_3. aa.15	N	0 -o	268-290,1.26; 237-246,1.216; 44-73,1.187; 212-233,1.172; 122-146,1.171; 107-114,1.165; 255-265,1.137; 79-90,1.113; 297-336,1.107; 192-198,1.104; 148-155,1.082; 99-105,1.066; 179-185,1.057	Amidation 152-155; Asn_Glycosylation 80-83, 232-235; Ck2_Phospho_Site 16-19, 20-23, 24-27, 29-32, 57-60, 96-99, 120-123, 247-250, 268-271, 299-302, 318-321, 324-327; Myristyl 66-71, 117-122, 177-182; Pkc_Phospho_Site 82-84, 145-147, 181-183, 217-219, 242-244, 247-249, 296-298, 299-301, 333-335;
DEX0374_3. aa.16	N	0 -o	44-73,1.187; 122-146,1.171; 107-114,1.165; 79-90,1.113; 99-105,1.066	Amidation 152-155; Asn_Glycosylation 80-83; Camp_Phospho_Site 154-157; Ck2_Phospho_Site 16-19, 20-23, 24-27, 29-32, 57-60, 96-99, 120-123; Myristyl 66-71, 117-122; Pkc_Phospho_Site 82-84, 145-147;
DEX0374_3. aa.19	N	0 -o	193-215,1.26; 716-742,1.253; 162-171,1.216; 414-425,1.199; 29-39,1.197; 4-23,1.187; 517-529,1.181; 137-158,1.172; 47-71,1.171; 364-396,1.17; 665-699,1.16; 644-654,1.16; 269-283,1.159; 180-190,1.137; 505-511,1.135; 452-476,1.132; 757-765,1.132; 317-333,1.127; 622-	Amidation 77-80; Asn_Glycosylation 30-33, 157-160, 419-422, 437-440; Camp_Phospho_Site 432-435; Ck2_Phospho_Site 3-6, 45-48, 172-175, 193-196, 224-227, 243-246, 270-273, 280-283, 401-404, 443-446, 481-484, 649-652; Myristyl 16-21, 42-47, 102-107, 370-375, 594-599, 642-647; Pkc_Phospho_Site 32-34, 70-72, 106-108, 142-144, 167-169, 172-174, 221-223, 224-226,



SequenceID	Signal P	TMHMM	Antigenicity	PTM
			637,1.12; 579-586,1.12; 551-576,1.117; 478-486,1.117; 222-242,1.107; 117-123,1.104; 744-750,1.1; 706-713,1.094; 539-548,1.093; 436-445,1.092; 73-80,1.082; 337-346,1.08; 353-361,1.079; 258-264,1.074; 244-250,1.071; 602-611,1.066; 104-110,1.057	253-255, 280-282, 315-317, 463-465, 481-483, 494-496, 509-511, 769-771; Rgd 338-340, 381-383; Tyr_Phospho_Site 442-450, 580-588;
DEX0374_3. aa.22	N	0 -o	268-290,1.26; 791-817,1.253; 237-246,1.216; 852-865,1.216; 489-500,1.199; 44-73,1.187; 592-604,1.181; 212-233,1.172; 122-146,1.171; 831-848,1.17; 439-471,1.17; 107-114,1.165; 740-774,1.16; 719-729,1.16; 344-358,1.159; 255-265,1.137; 580-586,1.135; 527-551,1.132; 392-408,1.127; 697-712,1.12; 654-661,1.12; 626-651,1.117; 553-561,1.117; 79-90,1.113; 297-317,1.107; 192-198,1.104; 819-827,1.1; 781-788,1.094; 614-623,1.093; 511-520,1.092; 148-155,1.082; 412-421,1.08; 428-436,1.079; 333-339,1.074; 319-325,1.071; 677-686,1.066; 99-105,1.066; 179-185,1.057	Amidation 152-155; Asn_Glycosylation 80-83, 232-235, 494-497, 512-515; Camp_Phospho_Site 507-510; Ck2_Phospho_Site 16-19, 20-23, 24-27, 29-32, 57-60, 96-99, 120-123, 247-250, 268-271, 299-302, 318-321, 345-348, 355-358, 476-479, 518-521, 556-559, 724-727; Myristyl 66-71, 117-122, 177-182, 445-450, 669-674, 717-722; Pkc_Phospho_Site 82-84, 145-147, 181-183, 217-219, 242-244, 247-249, 296-298, 299-301, 328-330, 355-357, 390-392, 538-540, 556-558, 569-571, 584-586, 836-838, 869-871; Rgd 413-415, 456-458; Tyr_Phospho_Site 517-525, 655-663;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_3. aa.23	N	0 -o	268-290,1.26; 237-246,1.216; 489-500,1.199; 44-73,1.187; 592- 604,1.181; 212- 233,1.172; 791- 802,1.172; 122- 146,1.171; 439- 471,1.17; 107- 114,1.165; 740- 774,1.16; 719- 729,1.16; 344- 358,1.159; 255- 265,1.137; 580- 586,1.135; 527- 551,1.132; 392- 408,1.127; 811- 823,1.125; 697- 712,1.12; 654- 661,1.12; 626- 651,1.117; 553- 561,1.117; 79- 90,1.113; 297- 317,1.107; 192- 198,1.104; 781- 788,1.094; 614- 623,1.093; 511- 520,1.092; 148- 155,1.082; 412- 421,1.08; 428- 436,1.079; 333- 339,1.074; 319- 325,1.071; 677- 686,1.066; 99- 105,1.066; 179- 185,1.057	Amidation 152-155; Asn_Glycosylation 80- 83, 232-235, 494-497, 512-515, 812-815; Camp_Phospho_Site 507-510; Ck2_Phospho_Site 16- 19, 20-23, 24-27, 29- 32, 57-60, 96-99, 120- 123, 247-250, 268-271, 299-302, 318-321, 345- 348, 355-358, 476-479, 518-521, 556-559, 724- 727; Myristyl 66-71, 117-122, 177-182, 445- 450, 669-674, 717-722, 813-818; Pkc_Phospho_Site 82- 84, 145-147, 181-183, 217-219, 242-244, 247- 249, 296-298, 299-301, 328-330, 355-357, 390- 392, 538-540, 556-558, 569-571, 584-586, 814- 816; Rgd 413-415, 456-458; Tyr_Phospho_Site 517- 525, 655-663;
DEX0374_3. aa.24	N	0 -o	268-290,1.26; 237-246,1.216; 489-500,1.199; 44-73,1.187; 212- 233,1.172; 122- 146,1.171; 439- 471,1.17; 107- 114,1.165; 344- 358,1.159; 255- 265,1.137; 392- 408,1.127; 79- 90,1.113; 297- 317,1.107; 192- 198,1.104; 148- 155,1.082; 412- 421,1.08; 428- 436,1.079; 333- 339,1.074; 319- 325,1.071; 99-	Amidation 152-155; Asn_Glycosylation 80- 83, 232-235, 494-497, 512-515; Camp_Phospho_Site 507-510; Ck2_Phospho_Site 16- 19, 20-23, 24-27, 29- 32, 57-60, 96-99, 120- 123, 247-250, 268-271, 299-302, 318-321, 345- 348, 355-358, 476-479, 518-521; Myristyl 66- 71, 117-122, 177-182, 445-450; Pkc_Phospho_Site 82- 84, 145-147, 181-183, 217-219, 242-244, 247- 249, 296-298, 299-301,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			105,1.066; 179-185,1.057	328-330, 355-357, 390-392; Rgd 413-415, 456-458;
DEX0374_3. aa.25	N	0 -o	237-246,1.216; 44-73,1.187; 212-233,1.172; 122-146,1.171; 107-114,1.165; 255-266,1.165; 79-90,1.113; 192-198,1.104; 148-155,1.082; 99-105,1.066; 179-185,1.057	Amidation 152-155; Asn_Glycosylation 80-83, 232-235; Ck2_Phospho_Site 16-19, 20-23, 24-27, 29-32, 57-60, 96-99, 120-123, 247-250; Myristyl 66-71, 117-122, 177-182; Pkc_Phospho_Site 82-84, 145-147, 181-183, 217-219, 242-244, 247-249;
DEX0374_6. aa.3	N	0 -o	4-14,1.177; 18-53,1.164	
DEX0374_6. aa.5	Y	0 -o	157-173,1.165; 20-47,1.136; 50-61,1.125; 5-14,1.125; 108-115,1.106; 74-83,1.097; 175-182,1.093; 64-72,1.08; 221-228,1.079; 197-205,1.074; 141-147,1.043	Amidation 244-247; Asn_Glycosylation 221-224, 236-239; Camp_Phospho_Site 125-128, 130-133; Ck2_Phospho_Site 99-102, 110-113, 133-136, 164-167, 210-213, 296-299, 313-316, 318-321; Myristyl 26-31, 46-51, 51-56, 143-148, 148-153; Pkc_Phospho_Site 89-91, 110-112, 128-130, 133-135, 217-219, 318-320; Tyr_Phospho_Site 219-225;
DEX0374_6. aa.10	Y	0 -o	157-173,1.165; 20-47,1.136; 50-61,1.125; 5-14,1.125; 315-326,1.112; 367-375,1.109; 337-348,1.107; 108-115,1.106; 74-83,1.097; 350-359,1.093; 175-182,1.093; 379-391,1.09; 64-72,1.08; 221-228,1.079; 197-205,1.074; 141-147,1.043	Amidation 244-247; Asn_Glycosylation 221-224, 236-239; Camp_Phospho_Site 125-128, 130-133; Ck2_Phospho_Site 99-102, 110-113, 133-136, 164-167, 210-213, 296-299, 313-316, 319-322, 331-334, 363-366, 388-391; Myristyl 26-31, 46-51, 51-56, 143-148, 148-153, 364-369, 394-399; Pkc_Phospho_Site 89-91, 110-112, 128-130, 133-135, 217-219; Tyr_Phospho_Site 219-225;
DEX0374_6.	Y	0 -o	157-173,1.165; 309-323,1.158;	Amidation 244-247; Asn_Glycosylation

SequenceID	Signal P	TMHMM	Antigenicity	PTM
aa.11			20-47,1.136; 50-61,1.125; 5-14,1.125; 108-115,1.106; 74-83,1.097; 175-182,1.093; 64-72,1.08; 221-228,1.079; 197-205,1.074; 141-147,1.043	221-224, 236-239; Camp_Phospho_Site 125-128, 130-133; Ck2_Phospho_Site 99-102, 110-113, 133-136, 164-167, 210-213, 296-299, 313-316; Myristyl 26-31, 46-51, 51-56, 143-148, 148-153; Pkc_Phospho_Site 89-91, 110-112, 128-130, 133-135, 217-219; Tyr_Phospho_Site 219-225;
DEX0374_6. aa.12	Y	0 -o	157-173,1.165; 20-47,1.136; 50-61,1.125; 5-14,1.125; 108-115,1.106; 74-83,1.097; 175-182,1.093; 64-72,1.08; 141-147,1.043	Camp_Phospho_Site 125-128, 130-133; Ck2_Phospho_Site 99-102, 110-113, 133-136, 164-167; Myristyl 26-31, 46-51, 51-56, 143-148, 148-153; Pkc_Phospho_Site 89-91, 110-112, 128-130, 133-135;
DEX0374_6. aa.15	N	0 -i	79-101,1.237; 152-173,1.212; 41-61,1.159; 11-36,1.132; 117-125,1.085; 127-133,1.043	Asn_Glycosylation 15-18, 118-121, 128-131; Ck2_Phospho_Site 78-81, 139-142, 151-154, 159-162; Myristyl 23-28, 108-113, 119-124; Pkc_Phospho_Site 14-16, 130-132, 136-138, 143-145, 174-176;
DEX0374_6. aa.16	Y	0 -o	157-173,1.165; 20-47,1.136; 50-61,1.125; 5-14,1.125; 324-335,1.112; 376-384,1.109; 346-357,1.107; 407-426,1.107; 108-115,1.106; 74-83,1.097; 359-368,1.093; 175-182,1.093; 388-400,1.09; 64-72,1.08; 230-237,1.079; 428-437,1.072; 141-147,1.043	Amidation 253-256; Asn_Glycosylation 230-233, 245-248; Camp_Phospho_Site 125-128, 130-133, 429-432; Ck2_Phospho_Site 99-102, 110-113, 133-136, 164-167, 219-222, 305-308, 322-325, 328-331, 340-343, 372-375, 397-400, 420-423; Myristyl 26-31, 46-51, 51-56, 143-148, 148-153, 373-378, 403-408; Pkc_Phospho_Site 89-91, 110-112, 128-130, 133-135, 210-212, 226-228, 432-434; Tyr_Phospho_Site 228-234;
DEX0374_6.	Y	0 -o	157-173,1.165; 20-47,1.136; 50-	Amidation 244-247; Asn_Glycosylation

SequenceID	Signal P	TMHMM	Antigenicity	PTM
aa.17			61,1.125; 5-14,1.125; 329-342,1.123; 315-326,1.112; 108-115,1.106; 74-83,1.097; 175-182,1.093; 64-72,1.08; 221-228,1.079; 197-205,1.074; 141-147,1.043	221-224, 236-239; Camp_Phospho_Site 125-128, 130-133; Ck2_Phospho_Site 99-102, 110-113, 133-136, 164-167, 210-213, 296-299, 313-316, 319-322, 331-334, 363-366; Myristyl 26-31, 46-51, 51-56, 143-148, 148-153, 380-385; Pkc_Phospho_Site 89-91, 110-112, 128-130, 133-135, 217-219, 363-365, 384-386; Tyr_Phospho_Site 219-225;
DEX0374_16 .aa.4	N	0 -o	433-456,1.234; 375-384,1.204; 267-278,1.183; 57-76,1.183; 280-290,1.169; 126-134,1.168; 494-504,1.167; 410-424,1.166; 915-930,1.16; 149-168,1.155; 613-652,1.151; 464-481,1.15; 88-107,1.149; 110-121,1.142; 887-896,1.127; 304-319,1.127; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 520-541,1.114; 938-952,1.112; 851-863,1.111; 244-254,1.11; 388-395,1.103; 697-708,1.1; 483-490,1.097; 555-566,1.097; 598-606,1.092; 834-840,1.09; 259-265,1.078; 870-881,1.076; 141-147,1.068; 810-816,1.064; 658-664,1.061; 799-806,1.058; 760-773,1.054; 26-39,1.047	Amidation 461-464, 823-826; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-468, 754-757, 940-943; Camp_Phospho_Site 760-763; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512, 617-620, 658-661, 676-679, 681-684, 700-703, 812-815, 840-843, 853-856, 887-890, 934-937, 942-945; Glycosaminoglycan 846-849; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 732-737, 733-738, 753-758, 762-767, 833-838, 837-842, 888-893; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 630-632, 640-642, 669-671, 721-723, 759-761, 950-952; Tyr_Phospho_Site 57-65;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_16 .aa.6	N	0 -o	1237-1264,1.277; 1139-1177,1.255; 433-456,1.234; 1274-1298,1.224; 1777-1787,1.221; 1063-1131,1.204; 375-384,1.204; 1408-1424,1.197; 1606-1623,1.194; 1718-1736,1.193; 1181-1227,1.189; 1660-1668,1.185; 267-278,1.183; 57-76,1.183; 965- 983,1.175; 280- 290,1.169; 1532- 1551,1.169; 126- 134,1.168; 934- 950,1.168; 494- 504,1.167; 410- 424,1.166; 1553- 1566,1.165; 1020- 1037,1.164; 888- 899,1.164; 868- 883,1.16; 1350- 1371,1.156; 149- 168,1.155; 994- 1005,1.153; 464- 481,1.15; 88- 107,1.149; 110- 121,1.142; 1814- 1826,1.141; 1850- 1862,1.131; 1833- 1843,1.13; 840- 849,1.127; 304- 319,1.127; 41- 48,1.127; 231- 239,1.123; 1460- 1473,1.123; 4- 13,1.122; 1337- 1344,1.122; 189- 197,1.121; 1868- 1884,1.12; 1300- 1313,1.12; 1380- 1387,1.119; 1039- 1056,1.118; 1495- 1502,1.118; 1799- 1812,1.117; 520- 541,1.114; 1754- 1763,1.111; 804- 816,1.111; 908- 914,1.111; 244- 254,1.11; 1445- 1453,1.104; 388- 395,1.103; 1573-	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341- 344, 351-354, 357-360, 366-369, 390-393, 465- 468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42- 45, 201-204, 205-208, 217-220, 228-231, 230- 233, 241-244, 248-251, 314-317, 325-328, 330- 333, 509-512, 629-632, 634-637, 653-656, 765- 768, 793-796, 806-809, 840-843, 887-890, 933- 936; Glycosaminoglycan 799-802; Leucine_Zipper 947- 968; Myristyl 342- 347, 358-363, 362-367, 595-600, 598-603, 685- 690, 686-691, 706-711, 715-720, 786-791, 790- 795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213- 215, 230-232, 258-260, 259-261, 599-601, 622- 624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57- 65;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1579,1.101; 650-661,1.1; 483-490,1.097; 555-566,1.097; 920-926,1.093; 598-606,1.092; 787-793,1.09; 1505-1513,1.081; 1478-1486,1.078; 259-265,1.078; 823-834,1.076; 1686-1694,1.069; 141-147,1.068; 763-769,1.064; 611-617,1.061; 1323-1330,1.059; 752-759,1.058; 1315-1321,1.055; 713-726,1.054; 26-39,1.047	
DEX0374_16 .aa.7	N	0 -o	805-832,1.277; 707-745,1.255; 4-24,1.234; 842-866,1.224; 1345-1355,1.221; 631-699,1.204; 976-992,1.197; 1174-1191,1.194; 1286-1304,1.193; 749-795,1.189; 1228-1236,1.185; 533-551,1.175; 1100-1119,1.169; 502-518,1.168; 62-72,1.167; 1121-1134,1.165; 588-605,1.164; 456-467,1.164; 436-451,1.16; 918-939,1.156; 562-573,1.153; 32-49,1.15; 1382-1394,1.141; 1418-1430,1.131; 1401-1411,1.13; 408-417,1.127; 1028-1041,1.123; 905-912,1.122; 1436-1452,1.12; 868-881,1.12; 948-955,1.119; 607-624,1.118; 1063-1070,1.118; 1367-1380,1.117; 88-109,1.114; 1322-	Amidation 29-32, 344-347; Asn_Glycosylation 33-36, 275-278, 535-538, 753-756, 987-990, 988-991; Camp_Phospho_Site 281-284; Ck2_Phospho_Site 77-80, 197-200, 202-205, 221-224, 333-336, 361-364, 374-377, 408-411, 455-458, 501-504, 704-707, 803-806, 838-841, 876-879, 893-896; Glycosaminoglycan 367-370; Leucine_Zipper 515-536; Myristyl 163-168, 166-171, 253-258, 254-259, 274-279, 283-288, 354-359, 358-363, 409-414, 474-479, 475-480, 627-632, 663-668, 722-727, 859-864; Pkc_Phospho_Site 167-169, 190-192, 242-244, 280-282, 562-564, 579-581, 704-706, 748-750, 752-754, 842-844, 845-847, 893-895, 905-907, 908-910; Prokar_Lipoprotein 984-994;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1331,1.111; 372-384,1.111; 476-482,1.111; 1013-1021,1.104; 1141-1147,1.101; 218-229,1.1; 51-58,1.097; 123-134,1.097; 488-494,1.093; 166-174,1.092; 355-361,1.09; 1073-1081,1.081; 1046-1054,1.078; 391-402,1.076; 1254-1262,1.069; 331-337,1.064; 179-185,1.061; 891-898,1.059; 320-327,1.058; 883-889,1.055; 281-294,1.054	
DEX0374_16 .aa.8	N	0 -o	1121-1148,1.277; 1023-1061,1.255; 317-340,1.234; 1158-1182,1.224; 1661-1671,1.221; 947-1015,1.204; 259-268,1.204; 1292-1308,1.197; 1490-1507,1.194; 1602-1620,1.193; 1065-1111,1.189; 1544-1552,1.185; 151-162,1.183; 57-81,1.183; 849-867,1.175; 164-174,1.169; 1416-1435,1.169; 818-834,1.168; 378-388,1.167; 294-308,1.166; 1437-1450,1.165; 904-921,1.164; 772-783,1.164; 752-767,1.16; 1234-1255,1.156; 878-889,1.153; 348-365,1.15; 1698-1710,1.141; 1734-1746,1.131; 1717-1727,1.13; 724-733,1.127; 188-203,1.127; 41-48,1.127; 115-123,1.123; 1344-	Amidation 345-348, 660-663; Asn_Glycosylation 109-112, 207-210, 225-228, 235-238, 241-244, 250-253, 274-277, 349-352, 591-594, 851-854; Camp_Phospho_Site 597-600; Ck2_Phospho_Site 42-45, 85-88, 89-92, 101-104, 112-115, 114-117, 125-128, 132-135, 198-201, 209-212, 214-217, 393-396, 513-516, 518-521, 537-540, 649-652, 677-680, 690-693, 724-727, 771-774, 817-820; Glycosaminoglycan 683-686; Leucine_Zipper 831-852; Myristyl 226-231, 242-247, 246-251, 479-484, 482-487, 569-574, 570-575, 590-595, 599-604, 670-675, 674-679, 725-730, 790-795, 791-796, 943-948, 979-984; Pkc_Phospho_Site 97-99, 114-116, 142-144, 143-145, 483-485, 506-508, 558-560, 596-598, 878-880, 895-897; Tyr_Phospho_Site 57-



SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1357,1.123; 4-13,1.122; 1221-1228,1.122; 1752-1768,1.12; 1184-1197,1.12; 1264-1271,1.119; 923-940,1.118; 1379-1386,1.118; 1683-1696,1.117; 404-425,1.114; 1638-1647,1.111; 688-700,1.111; 792-798,1.111; 128-138,1.11; 1329-1337,1.104; 272-279,1.103; 1457-1463,1.101; 534-545,1.1; 367-374,1.097; 439-450,1.097; 804-810,1.093; 482-490,1.092; 671-677,1.09; 1389-1397,1.081; 1362-1370,1.078; 143-149,1.078; 707-718,1.076; 1570-1578,1.069; 647-653,1.064; 495-501,1.061; 1207-1214,1.059; 636-643,1.058; 1199-1205,1.055; 597-610,1.054; 26-39,1.047	65;
DEX0374_16 .aa.9	N	0 -o	753-780,1.277; 655-693,1.255; 790-814,1.224; 1293-1303,1.221; 579-647,1.204; 924-940,1.197; 1122-1139,1.194; 1234-1252,1.193; 697-743,1.189; 1176-1184,1.185; 130-151,1.179; 481-499,1.175; 1048-1067,1.169; 450-466,1.168; 1069-1082,1.165; 536-553,1.164; 404-415,1.164; 384-399,1.16; 866-887,1.156; 510-521,1.153;	Amidation 178-181, 292-295; Asn_Glycosylation 56-59, 223-226, 483-486, 701-704, 935-938, 936-939; Camp_Phospho_Site 12-15, 229-232; Ck2_Phospho_Site 68-71, 93-96, 124-127, 281-284, 309-312, 322-325, 356-359, 403-406, 449-452, 652-655, 751-754, 786-789, 824-827, 841-844; Glycosaminoglycan 315-318; Leucine_Zipper 463-484; Myristyl 48-53, 53-58, 109-114, 116-121, 129-134, 133-138,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			65-79,1.149; 1330-1342,1.141; 1366-1378,1.131; 1349-1359,1.13; 356-365,1.127; 976-989,1.123; 853-860,1.122; 1384-1400,1.12; 816-829,1.12; 896-903,1.119; 555-572,1.118; 1011-1018,1.118; 1315-1328,1.117; 9-16,1.115; 1270- 1279,1.111; 320- 332,1.111; 424- 430,1.111; 19- 26,1.106; 961- 969,1.104; 1089- 1095,1.101; 159- 172,1.093; 436- 442,1.093; 81- 89,1.092; 303- 309,1.09; 1021- 1029,1.081; 994- 1002,1.078; 339- 350,1.076; 1202- 1210,1.069; 279- 285,1.064; 839- 846,1.059; 268- 275,1.058; 831- 837,1.055; 229- 242,1.054	137-142, 201-206, 202- 207, 222-227, 231-236, 302-307, 306-311, 357- 362, 422-427, 423-428, 575-580, 611-616, 670- 675, 807-812, 953-958, 954-959, 955-960, 959- 964; Pkc_Phospho_Site 9-11, 19-21, 90-92, 93-95, 120-122, 190- 192, 228-230, 510-512, 527-529, 652-654, 696- 698, 700-702, 790-792, 793-795, 841-843, 853- 855, 856-858, 975-977; Prokar_Lipoprotein 932-942;
DEX0374_16 .aa.11	N	0 -o	1237-1264,1.277; 1139-1177,1.255; 433-456,1.234; 1274-1298,1.224; 1799-1809,1.221; 1063-1131,1.204; 375-384,1.204; 1408-1424,1.197; 1606-1623,1.194; 1718-1736,1.193; 1181-1227,1.189; 1660-1668,1.185; 267-278,1.183; 57-76,1.183; 965- 983,1.175; 280- 290,1.169; 1532- 1551,1.169; 126- 134,1.168; 934- 950,1.168; 494- 504,1.167; 410- 424,1.166; 1553- 1566,1.165; 1020-	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341- 344, 351-354, 357-360, 366-369, 390-393, 465- 468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42- 45, 201-204, 205-208, 217-220, 228-231, 230- 233, 241-244, 248-251, 314-317, 325-328, 330- 333, 509-512, 629-632, 634-637, 653-656, 765- 768, 793-796, 806-809, 840-843, 887-890, 933- 936; Glycosaminoglycan 799-802; Leucine_Zipper 947- 968; Myristyl 342-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1037,1.164; 888- 899,1.164; 868- 883,1.16; 1350- 1371,1.156; 149- 168,1.155; 994- 1005,1.153; 1746- 1772,1.151; 464- 481,1.15; 88- 107,1.149; 110- 121,1.142; 1836- 1848,1.141; 1872- 1884,1.131; 1855- 1865,1.13; 840- 849,1.127; 304- 319,1.127; 41- 48,1.127; 231- 239,1.123; 1460- 1473,1.123; 4- 13,1.122; 1337- 1344,1.122; 189- 197,1.121; 1890- 1906,1.12; 1300- 1313,1.12; 1380- 1387,1.119; 1039- 1056,1.118; 1495- 1502,1.118; 1821- 1834,1.117; 520- 541,1.114; 1776- 1785,1.111; 804- 816,1.111; 908- 914,1.111; 244- 254,1.11; 1445- 1453,1.104; 388- 395,1.103; 1573- 1579,1.101; 650- 661,1.1; 483- 490,1.097; 555- 566,1.097; 920- 926,1.093; 598- 606,1.092; 787- 793,1.09; 1505- 1513,1.081; 1478- 1486,1.078; 259- 265,1.078; 823- 834,1.076; 1686- 1694,1.069; 141- 147,1.068; 763- 769,1.064; 611- 617,1.061; 1323- 1330,1.059; 752- 759,1.058; 1315- 1321,1.055; 713- 726,1.054; 26- 39,1.047	347, 358-363, 362-367, 595-600, 598-603, 685- 690, 686-691, 706-711, 715-720, 786-791, 790- 795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213- 215, 230-232, 258-260, 259-261, 599-601, 622- 624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57- 65;
	N	0 -o	1237-1264,1.277;	Amidation 461-464,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_16 .aa.16			1139-1177,1.255; 433-456,1.234; 1274-1298,1.224; 1063-1131,1.204; 375-384,1.204; 1408-1424,1.197; 1606-1623,1.194; 1181-1227,1.189; 1660-1668,1.185; 267-278,1.183; 57-76,1.183; 965- 983,1.175; 280- 290,1.169; 1532- 1551,1.169; 126- 134,1.168; 934- 950,1.168; 494- 504,1.167; 410- 424,1.166; 1553- 1566,1.165; 1020- 1037,1.164; 888- 899,1.164; 868- 883,1.16; 1350- 1371,1.156; 149- 168,1.155; 994- 1005,1.153; 464- 481,1.15; 88- 107,1.149; 110- 121,1.142; 1686- 1701,1.141; 840- 849,1.127; 304- 319,1.127; 41- 48,1.127; 231- 239,1.123; 1460- 1473,1.123; 4- 13,1.122; 1337- 1344,1.122; 189- 197,1.121; 1300- 1313,1.12; 1380- 1387,1.119; 1039- 1056,1.118; 1495- 1502,1.118; 520- 541,1.114; 804- 816,1.111; 908- 914,1.111; 244- 254,1.11; 1445- 1453,1.104; 388- 395,1.103; 1573- 1579,1.101; 650- 661,1.1; 483- 490,1.097; 555- 566,1.097; 920- 926,1.093; 598- 606,1.092; 787- 793,1.09; 1505- 1513,1.081; 1478-	776-779; Asn_Glycosylation 225-228, 323-326, 341- 344, 351-354, 357-360, 366-369, 390-393, 465- 468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42- 45, 201-204, 205-208, 217-220, 228-231, 230- 233, 241-244, 248-251, 314-317, 325-328, 330- 333, 509-512, 629-632, 634-637, 653-656, 765- 768, 793-796, 806-809, 840-843, 887-890, 933- 936; Glycosaminoglycan 799-802; Leucine_Zipper 947- 968; Myristyl 342- 347, 358-363, 362-367, 595-600, 598-603, 685- 690, 686-691, 706-711, 715-720, 786-791, 790- 795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213- 215, 230-232, 258-260, 259-261, 599-601, 622- 624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57- 65;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1486,1.078; 259-265,1.078; 823-834,1.076; 141-147,1.068; 763-769,1.064; 611-617,1.061; 1323-1330,1.059; 752-759,1.058; 1315-1321,1.055; 713-726,1.054; 26-39,1.047	
DEX0374_16 .aa.17	N	0 -o	1139-1177,1.255; 433-456,1.234; 1063-1131,1.204; 375-384,1.204; 1181-1227,1.189; 267-278,1.183; 57-76,1.183; 965-983,1.175; 280-290,1.169; 126-134,1.168; 934-950,1.168; 494-504,1.167; 410-424,1.166; 1020-1037,1.164; 888-899,1.164; 868-883,1.16; 149-168,1.155; 994-1005,1.153; 464-481,1.15; 88-107,1.149; 110-121,1.142; 840-849,1.127; 304-319,1.127; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 1039-1056,1.118; 520-541,1.114; 804-816,1.111; 908-914,1.111; 244-254,1.11; 388-395,1.103; 650-661,1.1; 483-490,1.097; 555-566,1.097; 920-926,1.093; 598-606,1.092; 787-793,1.09; 259-265,1.078; 823-834,1.076; 141-147,1.068; 763-769,1.064; 611-617,1.061; 752-	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512, 629-632, 634-637, 653-656, 765-768, 793-796, 806-809, 840-843, 887-890, 933-936; Glycosaminoglycan 799-802; Leucine_Zipper 947-968; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 685-690, 686-691, 706-711, 715-720, 786-791, 790-795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 622-624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57-65;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			759,1.058; 713-726,1.054; 26-39,1.047	
DEX0374_16 .aa.18	N	0 -o	433-456,1.234; 375-384,1.204; 823-846,1.187; 267-278,1.183; 57-76,1.183; 280-290,1.169; 126-134,1.168; 494-504,1.167; 410-424,1.166; 149-168,1.155; 464-481,1.15; 88-107,1.149; 110-121,1.142; 304-319,1.127; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 520-541,1.114; 804-816,1.111; 244-254,1.11; 388-395,1.103; 650-661,1.1; 483-490,1.097; 555-566,1.097; 598-606,1.092; 787-793,1.09; 259-265,1.078; 141-147,1.068; 763-769,1.064; 611-617,1.061; 752-759,1.058; 713-726,1.054; 26-39,1.047	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-468, 707-710; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512, 629-632, 634-637, 653-656, 765-768, 793-796, 806-809; Glycosaminoglycan 799-802; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 685-690, 686-691, 706-711, 715-720, 786-791, 790-795; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 622-624, 674-676, 712-714, 840-842; Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.20	N	0 -o	259-281,1.186; 57-76,1.183; 126-134,1.168; 149-168,1.155; 88-107,1.149; 110-121,1.142; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 244-254,1.11; 141-147,1.068; 26-39,1.047	Asn_Glycosylation 225-228; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261; Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.21	N	0 -o	433-456,1.234; 375-384,1.204; 267-278,1.183; 57-76,1.183; 280-290,1.169; 126-	Amidation 461-464; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			134,1.168; 494-504,1.167; 410-424,1.166; 149-168,1.155; 464-481,1.15; 88-107,1.149; 110-121,1.142; 304-319,1.127; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 520-541,1.114; 244-254,1.11; 388-395,1.103; 483-490,1.097; 555-566,1.097; 598-604,1.092; 259-265,1.078; 141-147,1.068; 26-39,1.047	468; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601; Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.22	N	O -o	1284-1311,1.277; 1186-1224,1.255; 433-456,1.234; 1321-1345,1.224; 1824-1834,1.221; 1110-1178,1.204; 375-384,1.204; 1455-1471,1.197; 1653-1670,1.194; 1765-1783,1.193; 1228-1274,1.189; 1707-1715,1.185; 267-278,1.183; 57-76,1.183; 1012-1030,1.175; 280-290,1.169; 1579-1598,1.169; 126-134,1.168; 981-997,1.168; 494-504,1.167; 410-424,1.166; 1600-1613,1.165; 1067-1084,1.164; 935-946,1.164; 915-930,1.16; 1397-1418,1.156; 149-168,1.155; 1041-1052,1.153; 613-652,1.151; 464-481,1.15; 88-107,1.149; 110-121,1.142; 1861-1873,1.141; 1897-1909,1.131; 1880-	Amidation 461-464, 823-826; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-468, 754-757; Camp_Phospho_Site 760-763; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512, 617-620, 658-661, 676-679, 681-684, 700-703, 812-815, 840-843, 853-856, 887-890, 934-937, 980-983; Glycosaminoglycan 846-849; Leucine_Zipper 994-1015; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 732-737, 733-738, 753-758, 762-767, 833-838, 837-842, 888-893, 953-958, 954-959; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 630-632, 640-642, 669-671, 721-723, 759-761;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1890,1.13; 887- 896,1.127; 304- 319,1.127; 41- 48,1.127; 231- 239,1.123; 1507- 1520,1.123; 4- 13,1.122; 1384- 1391,1.122; 189- 197,1.121; 1915- 1931,1.12; 1347- 1360,1.12; 1427- 1434,1.119; 1086- 1103,1.118; 1542- 1549,1.118; 1846- 1859,1.117; 520- 541,1.114; 1801- 1810,1.111; 851- 863,1.111; 955- 961,1.111; 244- 254,1.11; 1492- 1500,1.104; 388- 395,1.103; 1620- 1626,1.101; 697- 708,1.1; 483- 490,1.097; 555- 566,1.097; 967- 973,1.093; 598- 606,1.092; 834- 840,1.09; 1552- 1560,1.081; 1525- 1533,1.078; 259- 265,1.078; 870- 881,1.076; 1733- 1741,1.069; 141- 147,1.068; 810- 816,1.064; 658- 664,1.061; 1370- 1377,1.059; 799- 806,1.058; 1362- 1368,1.055; 760- 773,1.054; 26- 39,1.047	Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.23	N	0 -o	570-597,1.277; 472-510,1.255; 607-631,1.224; 1110-1120,1.221; 396-464,1.204; 741-757,1.197; 939-956,1.194; 1051-1069,1.193; 514-560,1.189; 993-1001,1.185; 298-316,1.175; 865-884,1.169; 267-283,1.168;	Amidation 109-112; Asn_Glycosylation 40-43, 300-303, 518-521, 752-755, 753-756; Camp_Phospho_Site 46-49, 968-971; Ck2_Phospho_Site 98-101, 126-129, 139-142, 173-176, 220-223, 266-269, 469-472, 568-571, 603-606, 641-644, 658-661, 822-825, 832-835, 841-844, 862-865, 880-



SequenceID	Signal P	TMHMM	Antigenicity	PTM
			886-899,1.165; 353-370,1.164; 221-232,1.164; 201-216,1.16; 683-704,1.156; 327-338,1.153; 1147-1159,1.141; 1183-1195,1.131; 1166-1176,1.13; 173-182,1.127; 793-806,1.123; 670-677,1.122; 1201-1217,1.12; 633-646,1.12; 713-720,1.119; 372-389,1.118; 828-835,1.118; 1132-1145,1.117; 1087-1096,1.111; 137-149,1.111; 241-247,1.111; 778-786,1.104; 906-912,1.101; 253-259,1.093; 120-126,1.09; 838-846,1.081; 811-819,1.078; 156-167,1.076; 1019-1027,1.069; 96-102,1.064; 656-663,1.059; 85-92,1.058; 648- 654,1.055; 46- 59,1.054	883; Glycosaminoglycan 132-135; Leucine_Zipper 280- 301; Myristyl 18-23, 19-24, 39-44, 48-53, 119-124, 123-128, 174- 179, 239-244, 240-245, 392-397, 428-433, 487- 492, 624-629, 770-775, 771-776, 772-777, 776- 781, 889-894; Pkc_Phospho_Site 3-5, 45-47, 327-329, 344- 346, 469-471, 513-515, 517-519, 607-609, 610- 612, 658-660, 670-672, 673-675, 792-794, 841- 843, 862-864, 903-905, 996-998; Prokar_Lipoprotein 749-759;
DEX0374_16 .aa.24	N	0 -o	433-456,1.234; 1063-1123,1.204; 375-384,1.204; 267-278,1.183; 57-76,1.183; 965- 983,1.175; 280- 290,1.169; 126- 134,1.168; 934- 950,1.168; 494- 504,1.167; 410- 424,1.166; 1020- 1037,1.164; 888- 899,1.164; 868- 883,1.16; 149- 168,1.155; 994- 1005,1.153; 464- 481,1.15; 88- 107,1.149; 110- 121,1.142; 840- 849,1.127; 304- 319,1.127; 41-	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341- 344, 351-354, 357-360, 366-369, 390-393, 465- 468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42- 45, 201-204, 205-208, 217-220, 228-231, 230- 233, 241-244, 248-251, 314-317, 325-328, 330- 333, 509-512, 629-632, 634-637, 653-656, 765- 768, 793-796, 806-809, 840-843, 887-890, 933- 936; Glycosaminoglycan 799-802; Leucine_Zipper 947-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 1039-1056,1.118; 520-541,1.114; 804-816,1.111; 908-914,1.111; 244-254,1.11; 388-395,1.103; 650-661,1.1; 483-490,1.097; 555-566,1.097; 920-926,1.093; 598-606,1.092; 787-793,1.09; 259-265,1.078; 823-834,1.076; 141-147,1.068; 763-769,1.064; 611-617,1.061; 752-759,1.058; 713-726,1.054; 26-39,1.047	968; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 685-690, 686-691, 706-711, 715-720, 786-791, 790-795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 622-624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.25	N	0 -o	1237-1264,1.277; 1139-1177,1.255; 433-456,1.234; 1274-1298,1.224; 1777-1787,1.221; 1063-1131,1.204; 375-384,1.204; 1408-1424,1.197; 1606-1623,1.194; 1718-1736,1.193; 1181-1227,1.189; 1660-1668,1.185; 267-278,1.183; 57-76,1.183; 965-983,1.175; 280-290,1.169; 1532-1551,1.169; 126-134,1.168; 934-950,1.168; 494-504,1.167; 410-424,1.166; 1553-1566,1.165; 1020-1037,1.164; 888-899,1.164; 868-883,1.16; 1350-1371,1.156; 149-168,1.155; 994-1005,1.153; 464-481,1.15; 88-107,1.149; 110-121,1.142; 1814-	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512, 629-632, 634-637, 653-656, 765-768, 793-796, 806-809, 840-843, 887-890, 933-936; Glycosaminoglycan 799-802; Leucine_Zipper 947-968; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 685-690, 686-691, 706-711, 715-720, 786-791, 790-795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 622-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1826,1.141; 1850-1862,1.131; 1833-1843,1.13; 840-849,1.127; 304-319,1.127; 41-48,1.127; 231-239,1.123; 1460-1473,1.123; 4-13,1.122; 1337-1344,1.122; 189-197,1.121; 1868-1890,1.12; 1300-1313,1.12; 1380-1387,1.119; 1039-1056,1.118; 1495-1502,1.118; 1799-1812,1.117; 520-541,1.114; 1754-1763,1.111; 804-816,1.111; 908-914,1.111; 244-254,1.11; 1445-1453,1.104; 388-395,1.103; 1573-1579,1.101; 650-661,1.1; 483-490,1.097; 555-566,1.097; 920-926,1.093; 598-606,1.092; 787-793,1.09; 1505-1513,1.081; 1478-1486,1.078; 259-265,1.078; 823-834,1.076; 1686-1694,1.069; 141-147,1.068; 763-769,1.064; 611-617,1.061; 1323-1330,1.059; 752-759,1.058; 1315-1321,1.055; 713-726,1.054; 26-39,1.047	624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.26	N	0 -o	1237-1264,1.277; 1139-1177,1.255; 433-456,1.234; 1274-1298,1.224; 1757-1767,1.221; 1063-1131,1.204; 375-384,1.204; 1408-1424,1.197; 1606-1623,1.194; 1181-1227,1.189; 1660-1668,1.185;	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42-45, 201-204, 205-208,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			267-278,1.183; 57-76,1.183; 965- 983,1.175; 280- 290,1.169; 1532- 1551,1.169; 126- 134,1.168; 934- 950,1.168; 494- 504,1.167; 410- 424,1.166; 1553- 1566,1.165; 1020- 1037,1.164; 888- 899,1.164; 868- 883,1.16; 1350- 1371,1.156; 149- 166,1.155; 994- 1005,1.153; 464- 481,1.15; 88- 107,1.149; 110- 121,1.142; 1794- 1806,1.141; 1830- 1842,1.131; 1813- 1823,1.13; 840- 849,1.127; 304- 319,1.127; 41- 48,1.127; 231- 239,1.123; 1460- 1473,1.123; 4- 13,1.122; 1337- 1344,1.122; 189- 197,1.121; 1848- 1864,1.12; 1300- 1313,1.12; 1380- 1387,1.119; 1039- 1056,1.118; 1495- 1502,1.118; 1779- 1792,1.117; 520- 541,1.114; 1734- 1743,1.111; 804- 816,1.111; 908- 914,1.111; 244- 254,1.11; 1445- 1453,1.104; 388- 395,1.103; 1573- 1579,1.101; 650- 661,1.1; 483- 490,1.097; 555- 566,1.097; 920- 926,1.093; 598- 606,1.092; 787- 793,1.09; 1718- 1730,1.089; 1505- 1513,1.081; 1478- 1486,1.078; 259- 265,1.078; 823- 834,1.076; 1686-	217-220, 228-231, 230- 233, 241-244, 248-251, 314-317, 325-328, 330- 333, 509-512, 629-632, 634-637, 653-656, 765- 768, 793-796, 806-809, 840-843, 887-890, 933- 936; Glycosaminoglycan 799-802; Leucine_Zipper 947- 968; Myristyl 342- 347, 358-363, 362-367, 595-600, 598-603, 685- 690, 686-691, 706-711, 715-720, 786-791, 790- 795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213- 215, 230-232, 258-260, 259-261, 599-601, 622- 624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57- 65;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1694,1.069; 141-147,1.068; 763-769,1.064; 611-617,1.061; 1323-1330,1.059; 752-759,1.058; 1315-1321,1.055; 713-726,1.054; 26-39,1.047	
DEX0374_16 .aa.27	N	0 -o	1237-1264,1.277; 1139-1177,1.255; 1850-1874,1.248; 433-456,1.234; 1274-1298,1.224; 1777-1787,1.221; 1063-1131,1.204; 375-384,1.204; 1408-1424,1.197; 1606-1623,1.194; 1718-1736,1.193; 1181-1227,1.189; 1660-1668,1.185; 267-278,1.183; 57-76,1.183; 965-983,1.175; 280-290,1.169; 1532-1551,1.169; 126-134,1.168; 934-950,1.168; 494-504,1.167; 410-424,1.166; 1553-1566,1.165; 1020-1037,1.164; 888-899,1.164; 868-883,1.16; 1350-1371,1.156; 149-168,1.155; 994-1005,1.153; 464-481,1.15; 88-107,1.149; 110-121,1.142; 1814-1826,1.141; 1833-1843,1.13; 840-849,1.127; 304-319,1.127; 41-48,1.127; 231-239,1.123; 1460-1473,1.123; 4-13,1.122; 1337-1344,1.122; 189-197,1.121; 1880-1902,1.12; 1300-1313,1.12; 1380-1387,1.119; 1039-1056,1.118; 1495-	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393, 465-468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512, 629-632, 634-637, 653-656, 765-768, 793-796, 806-809, 840-843, 887-890, 933-936; Glycosaminoglycan 799-802; Leucine_Zipper 947-968; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 685-690, 686-691, 706-711, 715-720, 786-791, 790-795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 622-624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57-65;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1502,1.118; 1799- 1812,1.117; 520- 541,1.114; 1754- 1763,1.111; 804- 816,1.111; 908- 914,1.111; 244- 254,1.11; 1445- 1453,1.104; 388- 395,1.103; 1573- 1579,1.101; 650- 661,1.1; 483- 490,1.097; 555- 566,1.097; 920- 926,1.093; 598- 606,1.092; 787- 793,1.09; 1505- 1513,1.081; 1478- 1486,1.078; 259- 265,1.078; 823- 834,1.076; 1686- 1694,1.069; 141- 147,1.068; 763- 769,1.064; 611- 617,1.061; 1323- 1330,1.059; 752- 759,1.058; 1315- 1321,1.055; 713- 726,1.054; 26- 39,1.047	
DEX0374_16 .aa.28	N	0 -o	1237-1264,1.277; 1139-1177,1.255; 433-456,1.234; 1274-1298,1.224; 1777-1787,1.221; 1063-1131,1.204; 375-384,1.204; 1408-1424,1.197; 1606-1623,1.194; 1718-1736,1.193; 1181-1227,1.189; 1660-1668,1.185; 267-278,1.183; 57-76,1.183; 965- 983,1.175; 1833- 1862,1.171; 280- 290,1.169; 1532- 1551,1.169; 126- 134,1.168; 934- 950,1.168; 494- 504,1.167; 410- 424,1.166; 1553- 1566,1.165; 1020- 1037,1.164; 888- 899,1.164; 868- 883,1.16; 1350-	Amidation 461-464, 776-779; Asn_Glycosylation 225-228, 323-326, 341- 344, 351-354, 357-360, 366-369, 390-393, 465- 468, 707-710, 967-970; Camp_Phospho_Site 713-716; Ck2_Phospho_Site 42- 45, 201-204, 205-208, 217-220, 228-231, 230- 233, 241-244, 248-251, 314-317, 325-328, 330- 333, 509-512, 629-632, 634-637, 653-656, 765- 768, 793-796, 806-809, 840-843, 887-890, 933- 936; Glycosaminoglycan 799-802; Leucine_Zipper 947- 968; Myristyl 342- 347, 358-363, 362-367, 595-600, 598-603, 685- 690, 686-691, 706-711, 715-720, 786-791, 790-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			1371,1.156; 149- 168,1.155; 994- 1005,1.153; 464- 481,1.15; 88- 107,1.149; 110- 121,1.142; 1814- 1826,1.141; 840- 849,1.127; 304- 319,1.127; 41- 48,1.127; 231- 239,1.123; 1460- 1473,1.123; 4- 13,1.122; 1337- 1344,1.122; 189- 197,1.121; 1300- 1313,1.12; 1380- 1387,1.119; 1039- 1056,1.118; 1495- 1502,1.118; 1799- 1812,1.117; 520- 541,1.114; 1754- 1763,1.111; 804- 816,1.111; 908- 914,1.111; 244- 254,1.11; 1445- 1453,1.104; 388- 395,1.103; 1573- 1579,1.101; 650- 661,1.1; 483- 490,1.097; 555- 566,1.097; 920- 926,1.093; 598- 606,1.092; 787- 793,1.09; 1505- 1513,1.081; 1478- 1486,1.078; 259- 265,1.078; 823- 834,1.076; 1686- 1694,1.069; 141- 147,1.068; 1877- 1884,1.065; 763- 769,1.064; 611- 617,1.061; 1323- 1330,1.059; 752- 759,1.058; 1315- 1321,1.055; 713- 726,1.054; 26- 39,1.047	795, 841-846, 906-911, 907-912; Pkc_Phospho_Site 213- 215, 230-232, 258-260, 259-261, 599-601, 622- 624, 674-676, 712-714, 994-996; Tyr_Phospho_Site 57- 65;
DEX0374_16 .aa.29	N	0 -o	433-456,1.234; 375-384,1.204; 267-278,1.183; 57-76,1.183; 704- 727,1.177; 280- 290,1.169; 126- 134,1.168; 494-	Amidation 461-464; Asn_Glycosylation 225-228, 323-326, 341- 344, 351-354, 357-360, 366-369, 390-393, 465- 468, 762-765, 766-769, 803-806, 832-835;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			504,1.167; 410-424,1.166; 149-168,1.155; 464-481,1.15; 88-107,1.149; 110-121,1.142; 661-671,1.132; 304-319,1.127; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 520-541,1.114; 244-254,1.11; 769-776,1.108; 388-395,1.103; 650-659,1.1; 483-490,1.097; 852-858,1.097; 555-566,1.097; 598-606,1.092; 729-737,1.087; 783-790,1.082; 259-265,1.078; 673-681,1.075; 141-147,1.068; 743-750,1.067; 611-617,1.061; 26-39,1.047; 816-822,1.043	Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333, 509-512, 629-632, 634-637, 653-656, 685-688, 708-711, 715-718, 732-735, 751-754, 764-767, 768-771, 795-798, 799-802, 862-865; Myristyl 342-347, 358-363, 362-367, 595-600, 598-603, 809-814; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261, 599-601, 622-624, 676-678, 751-753, 768-770, 843-845, 851-853; Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.30	N	0 -o	375-384,1.204; 267-278,1.183; 57-76,1.183; 280-290,1.169; 126-134,1.168; 410-424,1.166; 149-168,1.155; 88-107,1.149; 110-121,1.142; 304-319,1.127; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 244-254,1.11; 388-395,1.103; 259-265,1.078; 141-147,1.068; 26-39,1.047	Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369, 390-393; Ck2_Phospho_Site 42-45, 201-204, 205-208, 217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333; Myristyl 342-347, 358-363, 362-367; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261; Tyr_Phospho_Site 57-65;
DEX0374_16 .aa.31	N	0 -o	267-278,1.183; 57-76,1.183; 280-290,1.169; 126-134,1.168; 389-410,1.166; 375-386,1.156; 149-	Asn_Glycosylation 225-228, 323-326, 341-344, 351-354, 357-360, 366-369; Ck2_Phospho_Site 42-45, 201-204, 205-208,



SequenceID	Signal P	TMHMM	Antigenicity	PTM
			168,1.155; 88-107,1.149; 110-121,1.142; 304-319,1.127; 41-48,1.127; 231-239,1.123; 4-13,1.122; 189-197,1.121; 244-254,1.11; 259-265,1.078; 141-147,1.068; 26-39,1.047	217-220, 228-231, 230-233, 241-244, 248-251, 314-317, 325-328, 330-333; Myristyl 342-347, 358-363, 362-367; Pkc_Phospho_Site 213-215, 230-232, 258-260, 259-261; Tyr_Phospho_Site 57-65;
DEX0374_17 .aa.3	N	0 -o	70-86,1.16; 8-27,1.141; 111-122,1.134; 43-49,1.133; 88-96,1.126; 55-64,1.096; 151-160,1.083; 133-139,1.078	Asn_Glycosylation 58-61; Camp_Phospho_Site 40-43, 180-183; Ck2_Phospho_Site 43-46; Myristyl 56-61; Pkc_Phospho_Site 116-118, 145-147, 156-158, 163-165, 178-180, 183-185, 194-196;
DEX0374_17 .aa.4	N	0 -o	13-28,1.173; 251-263,1.161; 143-159,1.16; 71-100,1.141; 184-195,1.134; 116-122,1.133; 31-48,1.132; 50-57,1.132; 224-244,1.13; 161-169,1.126; 128-137,1.096; 206-212,1.078	Asn_Glycosylation 131-134; Camp_Phospho_Site 113-116; Ck2_Phospho_Site 69-72, 116-119, 251-254; Myristyl 9-14, 57-62, 66-71, 129-134; Pkc_Phospho_Site 189-191, 218-220, 229-231, 246-248;
DEX0374_17 .aa.5	N	0 -o	201-241,1.167; 178-196,1.161; 70-86,1.16; 8-27,1.141; 111-122,1.134; 43-49,1.133; 151-171,1.13; 88-96,1.126; 55-64,1.096; 133-139,1.078	Asn_Glycosylation 58-61; Camp_Phospho_Site 40-43; Ck2_Phospho_Site 43-46, 178-181, 201-204, 202-205, 247-250; Myristyl 56-61, 236-241; Pkc_Phospho_Site 116-118, 145-147, 156-158, 173-175;
DEX0374_17 .aa.6	N	1 - i65- 87o	64-85,1.27; 47-62,1.143; 20-30,1.073	Ck2_Phospho_Site 16-19; Pkc_Phospho_Site 21-23, 25-27; Prokar_Lipoprotein 79-89;
DEX0374_17 .aa.7	N	0 -o	151-165,1.22; 70-86,1.16; 8-27,1.141; 111-122,1.134; 43-49,1.133; 88-96,1.126; 55-64,1.096; 133-	Asn_Glycosylation 58-61; Camp_Phospho_Site 40-43; Ck2_Phospho_Site 43-46, 165-168; Myristyl 56-61; Pkc_Phospho_Site 116-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			139,1.078	118, 145-147, 156-158;
DEX0374_17 .aa.9	N	0 -o	95-107,1.161; 28-39,1.134; 68-88,1.13; 5-13,1.118; 50-56,1.078	Ck2_Phospho_Site 5-8, 95-98; Pkc_Phospho_Site 5-7, 33-35, 62-64, 73-75, 90-92;
DEX0374_24 .aa.2	N	0 -o	179-199,1.293; 333-362,1.171; 255-273,1.171; 217-230,1.16; 278-286,1.14; 24-40,1.122; 232-246,1.104; 104-117,1.102; 93-99,1.093; 304-314,1.092; 140-146,1.09; 291-297,1.078; 316-324,1.063; 129-135,1.043	Amidation 152-155; Camp_Phospho_Site 104-107; Ck2_Phospho_Site 356-359; Glycosaminoglycan 156-159; Myristyl 54-59, 58-63, 64-69, 78-83, 79-84, 161-166, 165-170, 215-220, 347-352; Pkc_Phospho_Site 14-16, 75-77, 93-95, 129-131, 156-158, 212-214, 321-323; Prokar_Lipoprotein 222-232;
DEX0374_24 .aa.3	Y	0 -o	4-23,1.293; 157-187,1.171; 79-97,1.171; 41-54,1.16; 102-110,1.14; 243-249,1.136; 56-70,1.104; 128-138,1.092; 115-121,1.078; 140-148,1.063; 280-286,1.021	Amidation 231-234, 270-273, 332-335; Asn_Glycosylation 310-313; Camp_Phospho_Site 234-237; Ck2_Phospho_Site 180-183, 282-285, 294-297, 320-323, 328-331; Myristyl 39-44, 171-176, 196-201, 202-207, 265-270, 304-309; Pkc_Phospho_Site 36-38, 145-147, 279-281, 284-286, 312-314, 319-321, 320-322; Prokar_Lipoprotein 46-56;
DEX0374_27 .aa.2	N	0 -o	4-25,1.182; 27-38,1.133; 43-51,1.132	Pkc_Phospho_Site 13-15, 28-30;
DEX0374_35 .aa.2	N	0 -o	15-57,1.21; 64-72,1.14; 118-138,1.081; 108-114,1.08; 81-90,1.055	Glycosaminoglycan 75-78; Myristyl 107-112; Pkc_Phospho_Site 119-121;
DEX0374_39 .aa.3	N	0 -o	28-40,1.189; 4-21,1.098	Ck2_Phospho_Site 26-29; Pkc_Phospho_Site 14-16, 19-21;
DEX0374_43 .aa.3	N	0 -o	26-72,1.133; 85-107,1.112	Ck2_Phospho_Site 118-121; Myristyl 9-14, 72-77; Pkc_Phospho_Site 40-42, 44-46, 111-113;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_45 .aa.2	Y	0 -i	101-129,1.21; 37-60,1.166; 91-99,1.111; 131-138,1.098; 10-21,1.085; 71-77,1.083	Ck2_Phospho_Site 22-25, 84-87; Prokar_Lipoprotein 50-60;
DEX0374_53 .aa.3	N	0 -o	611-626,1.248; 446-459,1.214; 952-962,1.204; 247-266,1.193; 639-649,1.16; 123-133,1.146; 666-685,1.141; 748-760,1.139; 387-395,1.131; 303-310,1.129; 180-187,1.128; 711-736,1.126; 474-483,1.124; 862-873,1.124; 408-423,1.123; 832-847,1.117; 236-242,1.112; 57-69,1.108; 509-517,1.105; 776-788,1.102; 158-165,1.101; 223-230,1.095; 807-819,1.091; 593-606,1.091; 191-199,1.088; 291-297,1.083; 269-276,1.079; 13-34,1.075; 141-153,1.069; 522-530,1.068; 82-88,1.064; 336-347,1.061; 548-554,1.061; 106-118,1.06; 91-99,1.056; 821-827,1.046; 431-439,1.037; 168-174,1.033; 561-567,1.032	Amidation 195-198, 227-230, 304-307, 402-405; Asn_Glycosylation 769-772; Camp_Phospho_Site 306-309, 372-375, 528-531; Ck2_Phospho_Site 31-34, 135-138, 236-239, 321-324, 328-331, 363-366, 375-378, 383-386, 464-467, 477-480, 505-508, 573-576, 650-653, 739-742, 765-768, 796-799, 893-896, 894-897, 895-898, 899-902; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279-284, 356-361, 440-445, 549-554, 632-637, 890-895, 907-912, 946-951, 947-952, 949-954; Pkc_Phospho_Site 70-72, 80-82, 84-86, 135-137, 172-174, 195-197, 221-223, 301-303, 316-318, 328-330, 345-347, 371-373, 400-402, 468-470, 521-523, 541-543, 714-716, 729-731, 744-746, 851-853; Rgd 183-185, 954-956;
DEX0374_53 .aa.4	N	0 -o	66-81,1.248; 94-104,1.16; 166-199,1.143; 15-38,1.142; 121-140,1.141; 48-61,1.091	Ck2_Phospho_Site 17-20, 105-108, 202-205; Myristyl 34-39, 87-92; Pkc_Phospho_Site 45-47, 169-171, 184-186;
DEX0374_53 .aa.6	N	0 -o	89-100,1.204; 4-11,1.124	Ck2_Phospho_Site 30-33, 31-34, 32-35, 36-39; Myristyl 27-32, 44-49, 83-88, 84-89,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_53 .aa.7	N	0 -o	611-626,1.248; 446-459,1.214; 944-954,1.204; 247-266,1.193; 639-649,1.16; 123-133,1.146; 666-685,1.141; 748-760,1.139; 387-395,1.131; 303-310,1.129; 180-187,1.128; 711-736,1.126; 474-483,1.124; 854-865,1.124; 408-423,1.123; 236-242,1.112; 57-69,1.108; 509- 517,1.105; 776- 788,1.102; 158- 165,1.101; 223- 230,1.095; 807- 819,1.091; 593- 606,1.091; 191- 199,1.088; 291- 297,1.083; 269- 276,1.079; 13- 34,1.075; 141- 153,1.069; 522- 530,1.068; 82- 88,1.064; 336- 347,1.061; 548- 554,1.061; 106- 118,1.06; 91- 99,1.056; 821- 827,1.046; 431- 439,1.037; 168- 174,1.033; 561- 567,1.032	86-91; Rgd 91-93; Amidation 195-198, 227-230, 304-307, 402- 405; Asn_Glycosylation 769-772; Camp_Phospho_Site 306-309, 372-375, 528- 531; Ck2_Phospho_Site 31-34, 135-138, 236- 239, 321-324, 328-331, 363-366, 375-378, 383- 386, 464-467, 477-480, 505-508, 573-576, 650- 653, 739-742, 765-768, 796-799, 885-888, 886- 889, 887-890, 891-894; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279- 284, 356-361, 440-445, 549-554, 632-637, 835- 840, 882-887, 899-904, 938-943, 939-944, 941- 946; Pkc_Phospho_Site 70-72, 80-82, 84-86, 135-137, 172-174, 195- 197, 221-223, 301-303, 316-318, 328-330, 345- 347, 371-373, 400-402, 468-470, 521-523, 541- 543, 714-716, 729-731, 744-746, 843-845; Rgd 183-185, 946-948;
DEX0374_53 .aa.8	N	0 -o	611-626,1.248; 446-459,1.214; 247-266,1.193; 639-649,1.16; 123-133,1.146; 666-685,1.141; 748-760,1.139; 387-395,1.131; 303-310,1.129; 180-187,1.128; 711-736,1.126; 474-483,1.124; 408-423,1.123; 236-242,1.112; 57-69,1.108; 509- 517,1.105; 776-	Amidation 195-198, 227-230, 304-307, 402- 405; Asn_Glycosylation 769-772; Camp_Phospho_Site 306-309, 372-375, 528- 531; Ck2_Phospho_Site 31-34, 135-138, 236- 239, 321-324, 328-331, 363-366, 375-378, 383- 386, 464-467, 477-480, 505-508, 573-576, 650- 653, 739-742, 765-768, 796-799; Glycosaminoglycan 221-224; Myristyl

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			788,1.102; 158-165,1.101; 223-230,1.095; 807-819,1.091; 593-606,1.091; 191-199,1.088; 291-297,1.083; 269-276,1.079; 13-34,1.075; 141-153,1.069; 522-530,1.068; 82-88,1.064; 336-347,1.061; 548-554,1.061; 106-118,1.06; 91-99,1.056; 821-827,1.046; 431-439,1.037; 168-174,1.033; 561-567,1.032	129-134, 142-147, 279-284, 356-361, 440-445, 549-554, 632-637; Pkc_Phospho_Site 70-72, 80-82, 84-86, 135-137, 172-174, 195-197, 221-223, 301-303, 316-318, 328-330, 345-347, 371-373, 400-402, 468-470, 521-523, 541-543, 714-716, 729-731, 744-746; Rgd 183-185;
DEX0374_53 .aa.10	N	0 -o	123-138,1.248; 456-466,1.204; 151-161,1.16; 178-197,1.141; 260-272,1.139; 223-248,1.126; 366-377,1.124; 21-29,1.105; 288-300,1.102; 319-331,1.091; 105-118,1.091; 34-42,1.068; 60-66,1.061; 333-339,1.046; 73-79,1.032	Asn_Glycosylation 281-284; Camp_Phospho_Site 40-43; Ck2_Phospho_Site 17-20, 85-88, 162-165, 251-254, 277-280, 308-311, 397-400, 398-401, 399-402, 403-406; Myristyl 61-66, 144-149, 347-352, 394-399, 411-416, 450-455, 451-456, 453-458; Pkc_Phospho_Site 33-35, 53-55, 226-228, 241-243, 256-258, 355-357; Rgd 458-460;
DEX0374_53 .aa.11	N	0 -o	238-248,1.204; 42-54,1.139; 5-30,1.126; 148-159,1.124; 70-82,1.102; 101-113,1.091; 127-133,1.053; 115-121,1.046	Asn_Glycosylation 63-66; Ck2_Phospho_Site 33-36, 59-62, 90-93, 179-182, 180-183, 181-184, 185-188; Myristyl 129-134, 176-181, 193-198, 232-237, 233-238, 235-240; Pkc_Phospho_Site 5-7, 23-25, 38-40, 137-139; Rgd 240-242;
DEX0374_53 .aa.12	N	0 -o	611-626,1.248; 446-459,1.214; 247-266,1.193; 639-649,1.16; 123-133,1.146; 666-685,1.141; 387-395,1.131; 303-310,1.129;	Amidation 195-198, 227-230, 304-307, 402-405; Camp_Phospho_Site 306-309, 372-375, 528-531; Ck2_Phospho_Site 31-34, 135-138, 236-239, 321-324, 328-331, 363-366, 375-378, 383-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			180-187,1.128; 474-483,1.124; 408-423,1.123; 236-242,1.112; 57-69,1.108; 509- 517,1.105; 158- 165,1.101; 223- 230,1.095; 593- 606,1.091; 191- 199,1.088; 291- 297,1.083; 269- 276,1.079; 13- 34,1.075; 141- 153,1.069; 522- 530,1.068; 82- 88,1.064; 336- 347,1.061; 548- 554,1.061; 106- 118,1.06; 91- 99,1.056; 431- 439,1.037; 168- 174,1.033; 561- 567,1.032	386, 464-467, 477-480, 505-508, 573-576, 650- 653; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279- 284, 356-361, 440-445, 549-554, 632-637; Pkc_Phospho_Site 70- 72, 80-82, 84-86, 135- 137, 172-174, 195-197, 221-223, 301-303, 316- 318, 328-330, 345-347, 371-373, 400-402, 468- 470, 521-523, 541-543; Rgd 183-185;
DEX0374_53 .aa.13	N	0 -o	611-626,1.248; 683-694,1.243; 446-459,1.214; 247-266,1.193; 639-649,1.16; 123-133,1.146; 674-681,1.132; 387-395,1.131; 303-310,1.129; 180-187,1.128; 474-483,1.124; 408-423,1.123; 236-242,1.112; 57-69,1.108; 509- 517,1.105; 158- 165,1.101; 223- 230,1.095; 593- 606,1.091; 191- 199,1.088; 291- 297,1.083; 269- 276,1.079; 13- 34,1.075; 141- 153,1.069; 522- 530,1.068; 82- 88,1.064; 336- 347,1.061; 548- 554,1.061; 106- 118,1.06; 91- 99,1.056; 431- 439,1.037; 168- 174,1.033; 561- 567,1.032	Amidation 195-198, 227-230, 304-307, 402- 405; Camp_Phospho_Site 306-309, 372-375, 528- 531; Ck2_Phospho_Site 31-34, 135-138, 236- 239, 321-324, 328-331, 363-366, 375-378, 383- 386, 464-467, 477-480, 505-508, 573-576, 650- 653; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279- 284, 356-361, 440-445, 549-554, 632-637, 673- 678, 678-683, 685-690, 693-698; Pkc_Phospho_Site 70- 72, 80-82, 84-86, 135- 137, 172-174, 195-197, 221-223, 301-303, 316- 318, 328-330, 345-347, 371-373, 400-402, 468- 470, 521-523, 541-543; Rgd 183-185;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_53 .aa.14	N	0 -o	238-248,1.204; 42-54,1.139; 5- 30,1.126; 148- 159,1.124; 70- 82,1.102; 101- 113,1.091; 127- 133,1.053; 115- 121,1.046	Asn_Glycosylation 63- 66; Ck2_Phospho_Site 33-36, 59-62, 90-93, 179-182, 180-183, 181- 184, 185-188; Myristyl 129-134, 176-181, 193- 198, 232-237, 233-238, 235-240; Pkc_Phospho_Site 5-7, 23-25, 38-40, 137-139; Rgd 240-242;
DEX0374_53 .aa.15	N	0 -o	446-459,1.214; 247-266,1.193; 123-133,1.146; 387-395,1.131; 303-310,1.129; 180-187,1.128; 474-483,1.124; 408-423,1.123; 236-242,1.112; 57-69,1.108; 548- 556,1.104; 158- 165,1.101; 533- 541,1.096; 223- 230,1.095; 191- 199,1.088; 291- 297,1.083; 517- 524,1.083; 269- 276,1.079; 13- 34,1.075; 141- 153,1.069; 82- 88,1.064; 336- 347,1.061; 106- 118,1.06; 91- 99,1.056; 431- 439,1.037; 168- 174,1.033	Amidation 195-198, 227-230, 304-307, 402- 405; Camp_Phospho_Site 306-309, 372-375; Ck2_Phospho_Site 31- 34, 135-138, 236-239, 321-324, 328-331, 363- 366; 375-378, 383-386, 464-467, 477-480, 505- 508; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279- 284, 356-361, 440-445, 523-528, 547-552; Pkc_Phospho_Site 70- 72, 80-82, 84-86, 135- 137, 172-174, 195-197, 221-223, 301-303, 316- 318, 328-330, 345-347, 371-373, 400-402, 468- 470, 527-529; Rgd 183-185;
DEX0374_53 .aa.16	N	0 -o	246-256,1.204; 42-54,1.139; 5- 30,1.126; 156- 167,1.124; 70- 82,1.102; 101- 113,1.091; 125- 132,1.057; 135- 141,1.053; 115- 121,1.046	Asn_Glycosylation 63- 66; Ck2_Phospho_Site 33-36, 59-62, 90-93, 187-190, 188-191, 189- 192, 193-196; Myristyl 184-189, 201-206, 240- 245, 241-246, 243-248; Pkc_Phospho_Site 5-7, 23-25, 38-40, 145-147; Rgd 248-250;
DEX0374_53 .aa.17	N	0 -o	21-29,1.105; 104- 118,1.091; 34- 42,1.068; 60- 66,1.061; 73- 79,1.032	Camp_Phospho_Site 40- 43; Ck2_Phospho_Site 17-20, 85-88; Myristyl 61-66; Pkc_Phospho_Site 33- 35, 53-55;
DEX0374_53	N	0 -o	66-81,1.248; 94- 104,1.16; 189-	Ck2_Phospho_Site 17- 20, 105-108, 125-128,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
.aa.18			222,1.143; 15-38,1.142; 141-149,1.136; 152-168,1.136; 122-139,1.11; 48-61,1.091	153-156; Myristyl 34-39, 87-92; Pkc_Phospho_Site 45-47, 127-129, 146-148, 207-209;
DEX0374_53 .aa.19	N	0 -o	570-585,1.248; 903-913,1.204; 247-266,1.193; 598-608,1.16; 123-133,1.146; 625-644,1.141; 707-719,1.139; 387-395,1.131; 303-310,1.129; 180-187,1.128; 670-695,1.126; 813-824,1.124; 408-423,1.123; 236-242,1.112; 57-69,1.108; 468-476,1.105; 735-747,1.102; 158-165,1.101; 223-230,1.095; 766-778,1.091; 552-565,1.091; 191-199,1.088; 291-297,1.083; 269-276,1.079; 13-34,1.075; 141-153,1.069; 481-489,1.068; 82-88,1.064; 336-347,1.061; 507-513,1.061; 106-118,1.06; 91-99,1.056; 780-786,1.046; 431-439,1.037; 168-174,1.033; 520-526,1.032	Amidation 195-198, 227-230, 304-307, 402-405; Asn_Glycosylation 728-731; Camp_Phospho_Site 306-309, 372-375, 487-490; Ck2_Phospho_Site 31-34, 135-138, 236-239, 321-324, 328-331, 363-366, 375-378, 383-386, 464-467, 532-535, 609-612, 698-701, 724-727, 755-758, 844-847, 845-848, 846-849, 850-853; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279-284, 356-361, 508-513, 591-596, 794-799, 841-846, 858-863, 897-902, 898-903, 900-905; Pkc_Phospho_Site 70-72, 80-82, 84-86, 135-137, 172-174, 195-197, 221-223, 301-303, 316-318, 328-330, 345-347, 371-373, 400-402, 480-482, 500-502, 673-675, 688-690, 703-705, 802-804; Rgd 183-185, 905-907;
DEX0374_53 .aa.20	N	0 -o	611-626,1.248; 446-459,1.214; 247-266,1.193; 639-649,1.16; 123-133,1.146; 666-685,1.141; 748-760,1.139; 387-395,1.131; 303-310,1.129; 180-187,1.128; 711-736,1.126; 474-483,1.124; 408-423,1.123;	Amidation 195-198, 227-230, 304-307, 402-405; Asn_Glycosylation 769-772; Camp_Phospho_Site 306-309, 372-375, 528-531; Ck2_Phospho_Site 31-34, 135-138, 236-239, 321-324, 328-331, 363-366, 375-378, 383-386, 464-467, 477-480, 505-508, 573-576, 650-653, 739-742, 765-768,



SequenceID	Signal P	TMHMM	Antigenicity	PTM
			236-242,1.112; 57-69,1.108; 509- 517,1.105; 776- 788,1.102; 158- 165,1.101; 223- 230,1.095; 807- 819,1.091; 593- 606,1.091; 191- 199,1.088; 291- 297,1.083; 269- 276,1.079; 13- 34,1.075; 141- 153,1.069; 522- 530,1.068; 82- 88,1.064; 336- 347,1.061; 548- 554,1.061; 106- 118,1.06; 91- 99,1.056; 834- 842,1.053; 821- 827,1.046; 431- 439,1.037; 168- 174,1.033; 561- 567,1.032	796-799; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279- 284, 356-361, 440-445, 549-554, 632-637, 835- 840; Pkc_Phospho_Site 70-72, 80-82, 84-86, 135-137, 172-174, 195- 197, 221-223, 301-303, 316-318, 328-330, 345- 347, 371-373, 400-402, 468-470, 521-523, 541- 543, 714-716, 729-731, 744-746, 843-845; Rgd 183-185;
DEX0374_53 .aa.21	N	0 -o	611-626,1.248; 446-459,1.214; 247-266,1.193; 800-814,1.187; 639-649,1.16; 123-133,1.146; 666-685,1.141; 748-760,1.139; 387-395,1.131; 303-310,1.129; 180-187,1.128; 711-736,1.126; 474-483,1.124; 408-423,1.123; 236-242,1.112; 57-69,1.108; 907- 922,1.107; 509- 517,1.105; 776- 788,1.102; 158- 165,1.101; 223- 230,1.095; 593- 606,1.091; 191- 199,1.088; 291- 297,1.083; 269- 276,1.079; 13- 34,1.075; 141- 153,1.069; 522- 530,1.068; 82- 88,1.064; 885- 893,1.063; 336- 347,1.061; 548-	Amidation 195-198, 227-230, 304-307, 402- 405, 845-848, 877-880; Asn_Glycosylation 769-772; Camp_Phospho_Site 306-309, 372-375, 528- 531, 861-864, 862-865; Ck2_Phospho_Site 31- 34, 135-138, 236-239, 321-324, 328-331, 363- 366, 375-378, 383-386, 464-467, 477-480, 505- 508, 573-576, 650-653, 739-742, 765-768, 796- 799; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279- 284, 356-361, 440-445, 549-554, 632-637, 845- 850, 849-854, 874-879, 902-907; Pkc_Phospho_Site 70- 72, 80-82, 84-86, 135- 137, 172-174, 195-197, 221-223, 301-303, 316- 318, 328-330, 345-347, 371-373, 400-402, 468- 470, 521-523, 541-543, 714-716, 729-731, 744- 746, 813-815, 834-836,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			554,1.061; 106-118,1.06; 91-99,1.056; 431-439,1.037; 168-174,1.033; 561-567,1.032	841-843, 857-859, 860-862, 877-879; Rgd 183-185;
DEX0374_53 .aa.22	N	0 -o	611-626,1.248; 446-459,1.214; 997-1007,1.204; 247-266,1.193; 687-705,1.188; 639-649,1.16; 730-744,1.153; 123-133,1.146; 666-685,1.141; 801-813,1.139; 387-395,1.131; 303-310,1.129; 180-187,1.128; 764-789,1.126; 474-483,1.124; 907-918,1.124; 408-423,1.123; 236-242,1.112; 709-719,1.11; 57-69,1.108; 509-517,1.105; 829-841,1.102; 158-165,1.101; 223-230,1.095; 860-872,1.091; 593-606,1.091; 191-199,1.088; 291-297,1.083; 269-276,1.079; 13-34,1.075; 141-153,1.069; 522-530,1.068; 82-88,1.064; 336-347,1.061; 548-554,1.061; 106-118,1.06; 91-99,1.056; 874-880,1.046; 431-439,1.037; 168-174,1.033; 561-567,1.032	Amidation 195-198, 227-230, 304-307, 402-405; Asn_Glycosylation 822-825; Camp_Phospho_Site 306-309, 372-375, 528-531; Ck2_Phospho_Site 31-34, 135-138, 236-239, 321-324, 328-331, 363-366, 375-378, 383-386, 464-467, 477-480, 505-508, 573-576, 650-653, 792-795, 818-821, 849-852, 938-941, 939-942, 940-943, 944-947; Glycosaminoglycan 221-224; Myristyl 129-134, 142-147, 279-284, 356-361, 440-445, 549-554, 632-637, 718-723, 888-893, 935-940, 952-957, 991-996, 992-997, 994-999; Pkc_Phospho_Site 70-72, 80-82, 84-86, 135-137, 172-174, 195-197, 221-223, 301-303, 316-318, 328-330, 345-347, 371-373, 400-402, 468-470, 521-523, 541-543, 767-769, 782-784, 797-799, 896-898; Rgd 183-185, 999-1001; Prokar_Lipoprotein 711-721;
DEX0374_53 .aa.23	N	0 -o	310-320,1.204; 4-18,1.157; 43-57,1.153; 114-126,1.139; 77-102,1.126; 220-231,1.124; 22-32,1.11; 142-154,1.102; 173-	Asn_Glycosylation 135-138; Ck2_Phospho_Site 105-108, 131-134, 162-165, 251-254, 252-255, 253-256, 257-260; Myristyl 31-36, 201-206, 248-253, 265-270, 304-309,

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			185,1.091; 187-193,1.046	305-310, 307-312; Pkc_Phospho_Site 80-82, 95-97, 110-112, 209-211; Rgd 312-314; Prokar_Lipoprotein 24-34;
DEX0374_53 .aa.25	N	0 -o	63-74,1.124; 208-220,1.111; 160-166,1.11; 115-126,1.109; 254-266,1.091; 145-155,1.087; 128-136,1.083; 39-50,1.074; 6-12,1.062; 245-252,1.02	Amidation 172-175; Camp_Phospho_Site 210-213; Ck2_Phospho_Site 94-97, 95-98, 96-99, 100-103, 161-164, 190-193, 194-197, 257-260; Myristyl 13-18, 91-96, 108-113, 198-203, 201-206, 205-210, 239-244, 252-257; Pkc_Phospho_Site 26-28, 172-174, 209-211, 261-263;
DEX0374_53 .aa.26	Y	0 -o	5-17,1.221; 25-46,1.165; 119-130,1.124; 265-276,1.111; 216-222,1.11; 172-182,1.109; 88-95,1.093; 64-77,1.091; 310-322,1.091; 202-211,1.087; 186-192,1.083; 98-104,1.053	Amidation 228-231; Camp_Phospho_Site 266-269; Ck2_Phospho_Site 53-56, 150-153, 151-154, 152-155, 156-159, 217-220, 246-249, 250-253, 313-316; Myristyl 147-152, 164-169, 254-259, 257-262, 261-266, 295-300, 308-313; Pkc_Phospho_Site 108-110, 228-230, 265-267, 317-319;
DEX0374_56 .aa.3	N	0 -o	33-79,1.271; 4-21,1.165; 97-106,1.14	Asn_Glycosylation 115-118; Ck2_Phospho_Site 24-27, 48-51, 116-119; Myristyl 33-38, 93-98, 100-105; Pkc_Phospho_Site 29-31, 34-36, 76-78;
DEX0374_56 .aa.4	N	0 -o	105-115,1.217; 501-510,1.204; 161-171,1.187; 336-345,1.175; 133-143,1.158; 349-374,1.156; 473-480,1.147; 308-315,1.147; 188-212,1.125; 376-398,1.125; 513-533,1.115; 24-39,1.115; 252-258,1.108; 12-	Zinc_Finger_C2h2 114-134, 142-162, 169-190, 170-190, 198-218, 288-308, 316-336, 344-364, 373-393, 453-473, 481-501, 509-529; Amidation 117-120, 319-322, 484-487; Asn_Glycosylation 13-16, 328-331, 335-338, 493-496, 500-503; Camp_Phospho_Site 119-122, 175-178, 321-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			18,1.102; 280-286,1.101; 445-451,1.101; 174-183,1.096; 93-101,1.095; 234-242,1.079; 222-231,1.078; 406-415,1.076; 458-467,1.072; 119-127,1.068; 265-272,1.055; 296-302,1.046; 45-54,1.035	324, 486-489; Ck2_Phospho_Site 83-86, 106-109, 197-200, 275-278, 536-539; Glycosaminoglycan 107-110; Myristyl 7-12, 12-17, 14-19, 70-75, 224-229, 259-264, 266-271, 269-274, 429-434; Pkc_Phospho_Site 76-78, 126-128, 150-152, 178-180, 324-326, 379-381, 424-426, 489-491, 517-519, 536-538;
DEX0374_56 .aa.9	N	1 - o44- 63i	46-65,1.197; 24-39,1.115; 12-18,1.102	Asn_Glycosylation 13-16; Myristyl 7-12, 12-17, 14-19; Pkc_Phospho_Site 62-64; Prokar_Lipoprotein 50-60;
DEX0374_56 .aa.12	N	0 -o	514-523,1.204; 174-184,1.187; 113-123,1.182; 349-358,1.175; 35-62,1.166; 146-156,1.158; 362-387,1.156; 486-493,1.147; 321-328,1.147; 74-80,1.128; 201-225,1.125; 389-411,1.125; 22-30,1.12; 526-546,1.115; 265-271,1.108; 293-299,1.101; 458-464,1.101; 187-196,1.096; 88-95,1.092; 247-255,1.079; 235-244,1.078; 419-428,1.076; 471-480,1.072; 132-140,1.068; 278-285,1.055; 309-315,1.046	Zinc_Finger_C2h2 155-175, 182-203, 183-203, 211-231, 301-321, 329-349, 357-377, 386-406, 466-486, 494-514, 522-542; Atp_Gtp_A 87-94; Amidation 130-133, 332-335, 497-500; Asn_Glycosylation 79-82, 341-344, 348-351, 506-509, 513-516; Camp_Phospho_Site 132-135, 188-191, 334-337, 499-502; Ck2_Phospho_Site 73-76, 210-213, 288-291, 549-552; Myristyl 68-73, 237-242, 272-277, 279-284, 282-287, 442-447; Pkc_Phospho_Site 103-105, 139-141, 163-165, 191-193, 337-339, 392-394, 437-439, 502-504, 530-532, 549-551;
DEX0374_56 .aa.13	N	0 -o	105-115,1.217; 161-171,1.187; 133-143,1.158; 174-194,1.115; 24-39,1.115; 12-18,1.102; 93-101,1.095; 119-127,1.068; 45-54,1.035	Zinc_Finger_C2h2 114-134, 142-162, 169-190, 170-190; Amidation 117-120; Asn_Glycosylation 13-16; Camp_Phospho_Site 119-122, 175-178; Ck2_Phospho_Site 83-86, 106-109, 197-200;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
				Glycosaminoglycan 107-110; Myristyl 7-12, 12-17, 14-19, 70-75; Pkc_Phospho_Site 76-78, 126-128, 150-152, 178-180, 197-199;
DEX0374_60 .aa.3	N	0 -o	35-61,1.222; 64-73,1.16; 101-112,1.122; 5-12,1.072	Asn_Glycosylation 106-109; Ck2_Phospho_Site 96-99; Myristyl 3-8, 46-51; Tyr_Phospho_Site 36-44;
DEX0374_70 .aa.2	N	0 -o	10-16,1.094; 32-49,1.092	Ck2_Phospho_Site 60-63; Myristyl 30-35, 33-38;
DEX0374_70 .aa.3	N	0 -i	10-16,1.094; 32-49,1.092	Myristyl 30-35, 33-38;
DEX0374_73 .aa.3	Y	7 - o20- 42i55- 77o81- 103i12 0- 142o15 2- 171i17 8- 200o22 4-246i	4-253,1.334; 282-318,1.14; 263-270,1.114	Leucine_Zipper 129-150; Myristyl 12-17, 237-242, 278-283; Pkc_Phospho_Site 15-17, 172-174, 175-177, 299-301; Prokar_Lipoprotein 64-74, 108-118, 110-120, 228-238;
DEX0374_73 .aa.8	N	0 -o	83-146,1.214; 5-77,1.186	Ck2_Phospho_Site 30-33, 77-80; Leucine_Zipper 69-90; Myristyl 110-115; Pkc_Phospho_Site 143-145;
DEX0374_73 .aa.9	N	0 -o	79-87,1.201; 180-214,1.193; 273-282,1.175; 4-27,1.173; 295-314,1.169; 56-76,1.168; 321-329,1.152; 237-245,1.151; 338-345,1.148; 140-155,1.147; 371-384,1.123; 89-104,1.121; 34-40,1.115; 167-176,1.112; 116-126,1.106; 255-261,1.098; 128-134,1.092; 361-368,1.084; 351-357,1.076	Asn_Glycosylation 35-38, 258-261, 343-346; Camp_Phospho_Site 220-223; Ck2_Phospho_Site 37-40, 138-141; Glycosaminoglycan 276-279; Myristyl 68-73, 174-179, 186-191, 209-214, 224-229, 272-277; Pkc_Phospho_Site 47-49, 153-155, 178-180, 218-220, 251-253, 289-291, 372-374;

SequenceID	Signal P	TMHMM	Antigenicity	PTM
DEX0374_73 .aa.11	N	0 -o	10-16,1.024	Pkc_Phospho_Site 19-21, 25-27;
DEX0374_73 .aa.12	N	0 -o	79-87,1.201; 166-175,1.188; 4-27,1.173; 56-76,1.168; 89-104,1.121; 34-40,1.115; 116-126,1.106; 128-139,1.098; 150-156,1.067	Asn_Glycosylation 35-38; Ck2_Phospho_Site 37-40; Myristyl 68-73, 148-153; Pkc_Phospho_Site 47-49;
DEX0374_80 .aa.2	N	1 - o704- 7261	607-619,1.309; 219-253,1.257; 703-725,1.239; 153-172,1.217; 107-150,1.215; 257-265,1.202; 9-35,1.178; 649-675,1.167; 621-640,1.166; 501-517,1.16; 363-375,1.157; 269-295,1.153; 308-315,1.147; 678-690,1.139; 474-481,1.128; 593-605,1.115; 344-350,1.111; 297-303,1.101; 455-465,1.099; 544-555,1.098; 421-430,1.091; 192-213,1.086; 582-588,1.076; 97-103,1.074; 532-538,1.073; 488-494,1.049; 178-184,1.033	Amidation 321-324; Asn_Glycosylation 82-85, 154-157, 524-527, 545-548; Camp_Phospho_Site 323-326, 337-340; Ck2_Phospho_Site 184-187, 201-204, 217-220, 340-343, 345-348, 398-401, 446-449, 529-532, 602-605, 670-673; Glycosaminoglycan 328-331; Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59, 55-60, 67-72, 80-85, 213-218, 331-336, 442-447, 489-494, 614-619, 662-667; Pkc_Phospho_Site 84-86, 217-219, 406-408, 446-448, 478-480, 573-575; Tyr_Phospho_Site 300-306; Pts_Hpr_Ser 474-489;
DEX0374_80 .aa.5	N	0 -o	565-577,1.309; 177-211,1.257; 107-151,1.215; 215-223,1.202; 607-651,1.191; 9-35,1.178; 579-598,1.166; 459-475,1.16; 321-333,1.157; 227-253,1.153; 266-273,1.147; 432-439,1.128; 551-563,1.115; 302-308,1.111; 255-261,1.101; 413-423,1.099; 502-	Amidation 279-282; Asn_Glycosylation 82-85, 482-485, 503-506; Camp_Phospho_Site 281-284, 295-298; Ck2_Phospho_Site 175-178, 298-301, 303-306, 356-359, 404-407, 487-490, 560-563; Glycosaminoglycan 286-289; Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59, 55-60, 67-72, 80-85, 171-176, 289-294, 400-405, 447-452, 572-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			513,1.098; 379-388,1.091; 540-546,1.076; 97-103,1.074; 490-496,1.073; 157-171,1.069; 446-452,1.049	577; Pkc_Phospho_Site 84-86, 175-177, 364-366, 404-406, 436-438, 531-533; Tyr_Phospho_Site 258-264; Pts_Hpr_Ser 432-447;
DEX0374_80 .aa.7	N	0 -o	607-619,1.309; 219-253,1.257; 153-172,1.217; 107-150,1.215; 257-265,1.202; 649-693,1.191; 9-35,1.178; 621-640,1.166; 501-517,1.16; 363-375,1.157; 269-295,1.153; 308-315,1.147; 474-481,1.128; 593-605,1.115; 344-350,1.111; 297-303,1.101; 455-465,1.099; 544-555,1.098; 421-430,1.091; 192-213,1.086; 582-588,1.076; 97-103,1.074; 532-538,1.073; 488-494,1.049; 178-184,1.033	Amidation 321-324; Asn_Glycosylation 82-85, 154-157, 524-527, 545-548; Camp_Phospho_Site 323-326, 337-340; Ck2_Phospho_Site 184-187, 201-204, 217-220, 340-343, 345-348, 398-401, 446-449, 529-532, 602-605; Glycosaminoglycan 328-331; Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59, 55-60, 67-72, 80-85, 213-218, 331-336, 442-447, 489-494, 614-619; Pkc_Phospho_Site 84-86, 217-219, 406-408, 446-448, 478-480, 573-575; Tyr_Phospho_Site 300-306; Pts_Hpr_Ser 474-489;
DEX0374_80 .aa.8	N	0 -i	11-55,1.191	
DEX0374_80 .aa.10	Y	0 -o	4-22,1.275; 30-62,1.191	Ck2_Phospho_Site 32-35; Pkc_Phospho_Site 27-29;
DEX0374_80 .aa.13	N	0 -o	219-253,1.257; 153-172,1.217; 107-150,1.215; 257-265,1.202; 9-35,1.178; 501-517,1.16; 363-375,1.157; 269-295,1.153; 308-315,1.147; 474-481,1.128; 344-350,1.111; 297-303,1.101; 455-465,1.099; 525-532,1.096; 421-430,1.091; 192-213,1.086; 97-103,1.074; 488-	Amidation 321-324; Asn_Glycosylation 82-85, 154-157, 524-527; Camp_Phospho_Site 323-326, 337-340; Ck2_Phospho_Site 184-187, 201-204, 217-220, 340-343, 345-348, 398-401, 446-449, 529-532; Glycosaminoglycan 328-331; Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59, 55-60, 67-72, 80-85, 213-218, 331-336, 442-447, 489-494; Pkc_Phospho_Site 84-

SequenceID	Signal P	TMHMM	Antigenicity	PTM
			494,1.049; 178-184,1.033	86, 217-219, 406-408, 446-448, 478-480; Tyr_Phospho_Site 300-306; Pts_Hpr_Ser 474-489;
DEX0374_80 .aa.14	N	0 -o	219-253,1.257; 153-172,1.217; 107-150,1.215; 257-265,1.202; 9-35,1.178; 269-295,1.153; 308-314,1.147; 297-303,1.101; 192-213,1.086; 97-103,1.074; 178-184,1.033	Asn_Glycosylation 82-85, 154-157; Ck2_Phospho_Site 184-187, 201-204, 217-220; Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59, 55-60, 67-72, 80-85, 213-218; Pkc_Phospho_Site 84-86, 217-219; Tyr_Phospho_Site 300-306;
DEX0374_80 .aa.16	N	0 -o	90-102,1.309; 132-176,1.191; 104-123,1.166; 76-88,1.115; 27-38,1.098; 65-71,1.076; 15-21,1.073	Asn_Glycosylation 28-31; Ck2_Phospho_Site 12-15, 85-88; Myristyl 97-102; Pkc_Phospho_Site 56-58;
DEX0374_80 .aa.18	N	0 -o	9-35,1.178; 57-74,1.161	Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59, 55-60; Pkc_Phospho_Site 76-78;
DEX0374_80 .aa.19	N	0 -o	219-253,1.257; 153-172,1.217; 107-150,1.215; 257-265,1.202; 488-499,1.188; 9-35,1.178; 363-375,1.157; 269-295,1.153; 308-315,1.147; 474-481,1.128; 344-350,1.111; 297-303,1.101; 455-465,1.099; 421-430,1.091; 192-213,1.086; 97-103,1.074; 178-184,1.033	Amidation 321-324; Asn_Glycosylation 82-85, 154-157; Camp_Phospho_Site 323-326, 337-340; Ck2_Phospho_Site 184-187, 201-204, 217-220, 340-343, 345-348, 398-401, 446-449; Glycosaminoglycan 328-331; Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59, 55-60, 67-72, 80-85, 213-218, 331-336, 442-447, 489-494; Pkc_Phospho_Site 84-86, 217-219, 406-408, 446-448, 478-480; Tyr_Phospho_Site 300-306; Pts_Hpr_Ser 474-489;
DEX0374_80 .aa.20	N	0 -o	107-148,1.215; 9-35,1.178; 97-103,1.074	Asn_Glycosylation 82-85; Myristyl 45-50, 48-53, 49-54, 51-56, 52-57, 53-58, 54-59,



SequenceID	Signal P	TMHMM	Antigenicity	PTM
				55-60, 67-72, 80-85; Pkc_Phospho_Site 84-86;
DEX0374_82 .aa.6	N	0 -o	88-110,1.23; 4-77,1.182; 138-159,1.156; 118-136,1.148; 79-86,1.094	Ck2_Phospho_Site 32-35; Myristyl 13-18, 69-74, 95-100, 136-141; Pkc_Phospho_Site 36-38, 59-61, 82-84;
DEX0374_82 .aa.7	N	0 -o	8-56,1.177; 88-100,1.176; 141-149,1.169; 114-122,1.165; 124-133,1.148; 179-186,1.121; 70-82,1.099; 167-174,1.081	Amidation 170-173; Ck2_Phospho_Site 131-134; Myristyl 19-24; Pkc_Phospho_Site 71-73, 155-157, 158-160, 178-180;
DEX0374_82 .aa.9	N	1 - i28- 50o	59-83,1.182; 21-56,1.171	Asn_Glycosylation 43-46; Ck2_Phospho_Site 12-15, 13-16;
DEX0374_85 .aa.5	N	2 - o10- 32i64- 86o	15-50,1.212; 62-91,1.182; 5-11,1.051	Myristyl 36-41, 47-52, 81-86; Pkc_Phospho_Site 57-59;
DEX0374_85 .aa.6	N	2 - o10- 32i64- 86o	15-50,1.212; 62-91,1.182; 5-11,1.051	Myristyl 36-41, 47-52, 81-86; Pkc_Phospho_Site 57-59;
DEX0374_85 .aa.11	N	0 -o	18-30,1.198; 37-49,1.153	Ck2_Phospho_Site 36-39; Myristyl 56-61, 67-72, 76-81;
DEX0374_85 .aa.20	N	0 -o	68-89,1.203; 121-141,1.144; 97-112,1.139; 52-58,1.055; 20-27,1.054; 7-13,1.052	Ck2_Phospho_Site 97-100, 121-124; Myristyl 58-63, 61-66, 63-68, 64-69; Pkc_Phospho_Site 7-9, 97-99;
DEX0374_86 .aa.2	N	0 -o	65-110,1.211; 116-124,1.16; 14-25,1.16; 49-63,1.113	Ck2_Phospho_Site 15-18, 29-32; Myristyl 105-110; Pkc_Phospho_Site 9-11, 48-50;
DEX0374_88 .aa.3	N	0 -o	118-131,1.139; 35-50,1.098; 76-93,1.086; 12-18,1.061	Asn_Glycosylation 107-110; Camp_Phospho_Site 102-105; Ck2_Phospho_Site 9-12, 24-27;
DEX0374_95 .aa.2	N	0 -o	90-119,1.156; 57-67,1.132; 18-29,1.106; 35-51,1.095; 4-10,1.089; 71-77,1.082	Glycosaminoglycan 19-22, 132-135; Myristyl 58-63, 128-133, 131-136; Pkc_Phospho_Site 19-21, 62-64, 73-75, 132-134;

**Example 2: Relative Quantitation of Gene Expression**

Real-Time quantitative PCR with fluorescent Taqman<sup>®</sup> probes is a quantitation detection system utilizing the 5'-3' nuclease activity of Taq DNA polymerase. The method uses an internal fluorescent oligonucleotide probe (Taqman<sup>®</sup>) labeled with a 5' reporter dye and a downstream, 3' quencher dye. During PCR, the 5'-3' nuclease activity of Taq DNA polymerase releases the reporter, whose fluorescence can then be detected by the laser detector of the Model 7700 Sequence Detection System (PE Applied Biosystems, Foster City, CA, USA). Amplification of an endogenous control is used to standardize the amount of sample RNA added to the reaction and normalize for Reverse Transcriptase (RT) efficiency. Either cyclophilin, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATPase, or 18S ribosomal RNA (rRNA) is used as this endogenous control. To calculate relative quantitation between all the samples studied, the target RNA levels for one sample were used as the basis for comparative results (calibrator). Quantitation relative to the "calibrator" can be obtained using the comparative method (User Bulletin #2: ABI PRISM 7700 Sequence Detection System).

The tissue distribution and the level of the target gene are evaluated for every sample in normal and cancer tissues. Total RNA is extracted from normal tissues, cancer tissues, and from cancers and the corresponding matched adjacent tissues. Subsequently, first strand cDNA is prepared with reverse transcriptase and the polymerase chain reaction is done using primers and Taqman<sup>®</sup> probes specific to each target gene. The results are analyzed using the ABI PRISM 7700 Sequence Detector. The absolute numbers are relative levels of expression of the target gene in a particular tissue compared to the calibrator tissue.

One of ordinary skill can design appropriate primers. The relative levels of expression of the HSNA versus normal tissues and other cancer tissues can then be determined. All the values are compared to the calibrator. Normal RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

The relative levels of expression of the HSNA in pairs of matched samples may also be determined. A matched pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. All the values are compared to the calibrator.

In the analysis of matching samples, the HSNA's that show a high degree of tissue specificity for the tissue of interest. These results confirm the tissue specificity results obtained with normal pooled samples. Further, the level of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual are compared.

- 5 This comparison provides an indication of specificity for the cancer state (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in matched samples tested are indicative of SEQ ID NO: 1-409 being a diagnostic marker for cancer.

### 10 **Example 3: Protein Expression**

- The HSNA is amplified by polymerase chain reaction (PCR) and the amplified DNA fragment encoding the HSNA is subcloned in pET-21d for expression in *E. coli*. In addition to the HSNA coding sequence, codons for two amino acids, Met-Ala, flanking the NH<sub>2</sub>-terminus of the coding sequence of HSNA, and six histidines, flanking the
- 15 COOH-terminus of the coding sequence of HSNA, are incorporated to serve as initiating Met/restriction site and purification tag, respectively.

An over-expressed protein band of the appropriate molecular weight may be observed on a Coomassie blue stained polyacrylamide gel. This protein band is confirmed by Western blot analysis using monoclonal antibody against 6X Histidine tag.

- 20 Large-scale purification of HSP is achieved using cell paste generated from 6-liter bacterial cultures, and purified using immobilized metal affinity chromatography (IMAC). Soluble fractions that are separated from total cell lysate were incubated with a nickel chelating resin. The column is packed and washed with five column volumes of wash buffer. HSP is eluted stepwise with various concentration imidazole buffers.

### 25 **Example 4: Fusion Proteins**

- The human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector. For example, if pC4 (Accession No.
- 30 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the

present invention, isolated by the PCR protocol described in Example 2, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced. If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if  
5 the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. *See, e.g.,* WO 96/34891.

#### **Example 5: Production of an Antibody from a Polypeptide**

In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such  
10 cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100, µg/ml of streptomycin. The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any  
15 suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP20), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands *et al.*, *Gastroenterology* 80: 225-232 (1981).

20 The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide. Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody  
25 which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic  
30 antibodies to the protein specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

**Example 6: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

RNA is isolated from individual patients or from a family of individuals that have a phenotype of interest. cDNA is then generated from these RNA samples using protocols known in the art. *See*, Sambrook (2001), *supra*. The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO: 1-409. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky *et al.*, *Science* 252(5006): 706-9 (1991). *See also* Sidransky *et al.*, *Science* 278(5340): 1054-9 (1997).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons are also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing. PCR products is cloned into T-tailed vectors as described in Holton *et al.*, *Nucleic Acids Res.*, 19: 1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements may also be determined. Genomic clones are nick-translated with digoxigenin deoxyuridine 5' triphosphate (Boehringer Mannheim), and FISH is performed as described in Johnson *et al.*, *Methods Cell Biol.* 35: 73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C-and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. Johnson (1991). Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

### **Example 7: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

Antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described above. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced. The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide. Next, 50 µl of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate. 75 µl of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution are added to each well and incubated 1 hour at room temperature.

The reaction is measured by a microtiter plate reader. A standard curve is prepared, using serial dilutions of a control sample, and polypeptide concentrations are plotted on the X-axis (log scale) and fluorescence or absorbance on the Y-axis (linear scale). The concentration of the polypeptide in the sample is calculated using the standard curve.

### **Example 8: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1, µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given

continuously, the secreted polypeptide is typically administered at a dose rate of about 1  $\mu\text{g/kg/hour}$  to about 50  $\text{mg/kg/hour}$ , either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U. S. Pat. No. 3,773,919, EP 58,481, the contents of which are hereby incorporated by reference herein in their entirety), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22: 547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15: 167-277 (1981), and R. Langer, Chem. Tech. 12: 98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE Epstein et al., Proc. Natl. Acad. Sci. USA 82: 3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324, the contents of which are hereby incorporated by reference herein in their entirety. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides. Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably, the carrier is a parenteral carrier, more preferably, a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e. g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container



having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1 % (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container (s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

#### **Example 9: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided above.

#### **Example 10: Method of Treating Increased Levels of the Polypeptide**

Antisense or RNAi technology are used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided  
5 above.

#### **Example 11: Method of Treatment Using Gene Therapy**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a  
10 subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of  
15 the flask and fresh media (e. g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks. pMV-7 (Kirschmeier, P. T. et al.,  
20 DNA, 7: 219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using  
25 PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 3. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the  
30 two fragments. The ligation mixture is then used to transform bacteria HB 101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+aml2 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now  
5 produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached  
10 producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media.

If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector  
15 that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

## 20 **Example 12: Method of Treatment Using Gene Therapy-In Vivo**

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide.

25 The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, Tabata H. *et al. Cardiovasc. Res.* 35 (3): 470-479 (1997); Chao J *et al. Pharmacol. Res.* 35 (6): 517-522 (1997); Wolff J. A. *Neuromuscul. Disord.* 7 (5):  
30 314-318 (1997), Schwartz B. *et al. Gene Ther.* 3 (5): 405-411 (1996); and Tsurumi Y. *et al. Circulation* 94 (12): 3281-3290 (1996); W0 90/11092, W0 98/11779; U. S. Patent No. 5,693,622; 5,705,151; 5,580,859, the contents of which are hereby incorporated by reference herein in their entirety.

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, hepatic, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

5       The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P. L. *et al. Ann. NY*  
10 *Acad. Sci.* 772: 126-139 (1995) and Abdallah B. *et al. Biol. Cell* 85 (1): 1-7 (1995)) which can be prepared by methods well known to those skilled in the art.

      The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art  
15 can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

20       The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, hepatic, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide  
25 matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They  
30 may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin

fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 µg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to hepatics or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle in vivo is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 µm cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection

may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice.

The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

5

### Example 13: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e. g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (I. e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., *Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver et al., *Biotechnology* 11: 1263-1270 (1993); Wright et al., *Biotechnology* 9: 830-834 (1991); and U. S. Pat. No. 4,873,191, the contents of which is hereby incorporated by reference herein in its entirety); retrovirus mediated gene transfer into germ lines (Van der Putten et al., *Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., *Cell* 56: 313-321 (1989)); electroporation of cells or embryos (Lo, 1983, *Mol Cell. Biol.* 3: 1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e. g., Ulmer et al., *Science* 259: 1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm mediated gene transfer (Lavitrano et al., *Cell* 57: 717-723 (1989). For a review of such techniques, see Gordon, "Transgenic Animals," *Intl. Rev. Cytol.* 115: 171-229 (1989).

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., *Nature* 380: 64-66 (1996); Wilmut et al., *Nature* 385: 810813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells,

I. e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al.,  
5 *Proc. Natl. Acad. Sci. USA* 89: 6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some  
10 nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et  
15 al. (Gu et al., *Science* 265: 103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished  
20 by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR).  
25 Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding  
30 strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous

transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### **Example 14: Knock-Out Animals**

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E. g., see Smithies et al., *Nature* 317: 230-234 (1985); Thomas & Capecchi, *Cell* 51: 503-512 (1987); Thompson et al., *Cell* 5: 313-321 (1989)) Alternatively, RNAi technology may be used. For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention in vivo. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e. g., see Thomas & Capecchi 1987 and Thompson 1989, supra). However, this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site in vivo using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e. g., knockouts) are administered to a



patient in vivo. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e. g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e. g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e. g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U. S. Patent No. 5,399,349; and Mulligan & Wilson, U. S. Patent No. 5,460,959, the contents of which are hereby incorporated by reference herein in their entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

While preferred illustrative embodiments of the present invention are described, one skilled in the art will appreciate that the present invention can be practiced by other than the described embodiments, which are presented for purposes of illustration only and not by way of limitation. The present invention is limited only by the claims that follow.

We claim:

1. An isolated nucleic acid molecule comprising:
  - (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 410-611;
  - 5 (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-409;
  - (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or
  - (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b).
- 10 2. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a cDNA.
- 15 3. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is genomic DNA.
4. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is an RNA.
- 20 5. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a mammalian nucleic acid molecule.
6. The nucleic acid molecule according to claim 5, wherein the nucleic acid molecule is a human nucleic acid molecule.
- 25 7. A method for determining the presence of a hepatic specific nucleic acid (HSNA) in a sample, comprising the steps of:
  - (a) contacting the sample with the nucleic acid molecule of SEQ ID NO: 1-409
  - 30 under conditions in which the nucleic acid molecule will selectively hybridize to a hepatic specific nucleic acid; and

(b) detecting hybridization of the nucleic acid molecule to a HSNA in the sample, wherein the detection of the hybridization indicates the presence of a HSNA in the sample.

- 5     8.     A vector comprising the nucleic acid molecule of claim 1.
9.     A host cell comprising the vector according to claim 8.
- 10    10.    A method for producing a polypeptide encoded by the nucleic acid molecule according to claim 1, comprising the steps of:
- 15        (a)     providing a host cell comprising the nucleic acid molecule operably linked to one or more expression control sequences, and
- (b)     incubating the host cell under conditions in which the polypeptide is produced.
11.    A polypeptide encoded by the nucleic acid molecule according to claim 1.
12.    An isolated polypeptide selected from the group consisting of:
- 20        (a)     a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 410-611 ; or
- (b)     a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-409.
- 25    13.    An antibody or fragment thereof that specifically binds to:
- (a)     a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 410-611 ; or
- 30        (b)     a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-409.
14.    A method for determining the presence of a hepatic specific protein in a sample, comprising the steps of:

- (a) contacting the sample with a suitable reagent under conditions in which the reagent will selectively interact with the hepatic specific protein comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 410-611; and
- 5 (b) detecting the interaction of the reagent with a hepatic specific protein in the sample, wherein the detection of binding indicates the presence of a hepatic specific protein in the sample.
15. A method for diagnosing or monitoring the presence and metastases of hepatic cancer in a patient, comprising the steps of:
- 10 (a) determining an amount of:
- (i) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 410-611;
- (ii) a nucleic acid molecule comprising a nucleic acid sequence of SEQ  
15 ID NO: 1-409;
- (iii) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (i) or (ii);
- (iv) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (i) or (ii);
- 20 (v) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 410-611 ; or
- (vi) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-409  
25 and;
- (b) comparing the amount of the determined nucleic acid molecule or the polypeptide in the sample of the patient to the amount of the hepatic specific marker in a normal control; wherein a difference in the amount of the nucleic acid molecule or the polypeptide in the sample compared to the amount of the nucleic  
30 acid molecule or the polypeptide in the normal control is associated with the presence of hepatic cancer.

16. A kit for detecting a risk of cancer or presence of cancer in a patient, said kit comprising a means for determining the presence of:

- (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 410-611;
- 5 (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-409;
- (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or
- (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b); or
- 10 (e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 410-611 ; or
- (f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule
- 15 comprising a nucleic acid sequence of SEQ ID NO: 1-409.

17. A method of treating a patient with hepatic cancer, comprising the step of administering a composition consisting of:

- (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 410-611;
- 20 (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-409;
- (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b);
- 25 (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b);
- (e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 410-611 ; or
- (f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule
- 30 comprising a nucleic acid sequence of SEQ ID NO: 1-409;

to a patient in need thereof, wherein said administration induces an immune response against the hepatic cancer cell expressing the nucleic acid molecule or polypeptide.

18. A vaccine comprising the polypeptide or the nucleic acid encoding the polypeptide of claim 12.

## 1

## SEQUENCE LISTING

<110> diaDexus, Inc.  
Sun, Yongming  
Liu, Chenghua

<120> Compositions and Methods Relating to Hepatic Specific Genes and Proteins

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6048

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26

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27

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&lt;213&gt; Homo sapien

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31

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&lt;213&gt; Homo sapien

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46

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 <213> Homo sapien

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caaggcccaa agaagtaaaa agacttgtct acaggagagt gcctctgagg accaacagga	180
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51

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 tcgtcctgtc agactagcgg agtttaagag agctgtgaaa gtagcaacag gacaagaact 1260  
 ctcaaacaat attttggaca ctgtctttaa gatctttgat ttggatgggtg atgaatgtct 1320  
 tagtcatgaa gagtttcttg ggggtgttaa aaacagaatg catcgagggt tatgggtacc 1380  
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 aaaagaagtc tggaaacaag ctggaaaagg tcttttttaa taaaagatat aatagtatgg 1500  
 caattatatt gttccaaatg tcaaaatttg tgatttttta gaagtacttg ctatttatct 1560  
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 gattcactga tttcttagac actctaatat gatatgcttt ctggaaggat aaaacaaata 1800  
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 taataggcta aatgaagtta aaaacttatt tcagattttt ctcatctgta ccttatatct 1920  
 cataaattta ttgcatattt tatgtcagta gcttagctgt ttattgtctt taaaataaca 1980  
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&lt;210&gt; 40

&lt;211&gt; 1490

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 40

cgcgcccga ccgtttgttt tatttgtaag tgctcagatt ttgaagtcag atggaccaag 60  
 gttcagatcc tgattgttcc agttagtaga ctttgggcaa actacataac ccctgaagcg 120  
 ttacttacct aagacttaga gaggctaagg tcatacacgt tataaagggc agaaccggaa 180  
 tttcagcatt aaaagtccat ctaactccaa aactctgtgc tcttactcag tgctatgtcc 240  
 actaataaaa ctttagcagaa gtggaccact taacagagta tgtagtctc ttcaagctgc 300  
 cacctcaaaa caccacaggc tgggcagctt aaacaataaa tttatttctc ttgcccagcc 360  
 tgcacacagc accttctcac tgtgcccttt gtgtggccat ttctgtgtgc acacagagag 420  
 aaagggacag agaaagctct gttgtctctt cctcttagaa tgatactagt ctctacggta 480  
 gaaaagaaag ttcatagtta acatttataa gattatttaa tgtacttaca aaattgtaat 540  
 aaaaactctt actttattag agcatttagt tggatgaatt caagtcatct tgccatttta 600  
 caaccactt ggaagacttt gctattgcca tgcagatgtt cagtttagct catcgtcctg 660



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tcagactagc ggagtttaag agagctgtga aagtagcaac aggacaagaa ctctcaaaca	720
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aagagtttct tggggtgtta aaaaacagaa tgcacgcagg tttatgggta ccacaacatc	840
agagtataca agaatactgg aagtgtgtga agaaagaaag cattaaagga gtaaaagaag	900
tctggaaaca agctggaaaa ggtctttttt aataaaagat ataatagtat ggcaattata	960
ttgttccaaa tgtcaaaatt tgtgattttt tagaagtact tgctattttat cttottaagt	1020
cttcattgat attctgtgtg aaataagcat gtcttgtact tgctttctga ttcataattt	1080
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gatttcttag acactctaata atgatatgct ttctggaagg ataaaacaaa tacatatggg	1260
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tattgcataat tttatgtcag tagcttagct gtttattgtc tttaaaataa catgtaaact	1440
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<210> 41  
 <211> 1321  
 <212> DNA  
 <213> Homo sapien

<400> 41	
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ttcaagacca gcctggccaa catggtgaaa ccccatctct actaaaaata caaaaactag	120
ctgggcgtgg tggcaggcgc ctgtaatccc agctattcag gaggccgagg caagagaatc	180
gcttgaaccc gggagacgga ggtttagtg agtcaagatc gtgccattgc actccagcct	240
gggcgacgag caagattcat ctcaaatata tgtttagagc attgattaaa ttacaatagc	300
tcatttgtct tgcagtgact ctcatgacat tcgtcggctt atggtttgaa tattttcttc	360
atgggtattt ttgtttttgt tttacttccc aaataataaa aatttggatt tgcttttact	420
tctcaaataa tgaaaattta gattaatttc acttagacta tttcacatag ttgataagtt	480
gttttatgtt tgtttttttag cggagtttaa gagagctgtg aaagtagcaa caggacaaga	540
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tcttagtcat gaagagtttc ttggggtgtt aaaaaacaga atgcatcgag gtttatgggt	660
accacaacat cagagtatac aagaatactg gaagtgtgtg aagaaagaaa gcattaaagg	720
agtaaaagaa gtctggaaac aagctggaaa aggtcttttt taataaaaga tataatagta	780

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tggcaattat attgttccaa atgtcaaaat ttgtgatttt ttagaagtac ttgctattta 840  
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 agtgattcac tgattttctta gacactctaa tatgatatgc tttctggaag gataaaacaa 1080  
 atacatatgg gaaaaagtag ttgagaccaa ggccagcatc aattccagac atcttcatgt 1140  
 tcctaatagg ctaaataag ttaaaaactt atttcagatt tttctcatct gtaccttata 1200  
 tctcataaat ttattgcata ttttatgtca gtagcttagc tgtttattgt ctttaaaata 1260  
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<210> 42  
 <211> 1601  
 <212> DNA  
 <213> Homo sapien

<400> 42  
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 caaacatatt aatattttat aagcttgcag ttatccaaca ccataaata tattccggga 180  
 aattaagcca gtcttttcag ttcacaattg agtgtagctg ggagtctoct tgccctttct 240  
 cagaagacat taaaaagaaa agctgtaaat cagtcataag aaaaagaaca tatataatct 300  
 ggagtagaat ttgcttcca cttggctaatt tttcatcagt gctatgctcc tgtgggtccc 360  
 cggatccaaa tatttcctaa cctttacott ttcattttgt tgagagtagt agtaatccac 420  
 atgtattttt agctaacaaa acacgtccat gaattagatt atttcttgaa gcttttcac 480  
 aaatattttg tggccttttt tttttttaat tttagccaat gttaaataca agcttttaggc 540  
 ttataattgt attctacata gctaaacaaa gttcaccaga aaaaaaggga aagattataa 600  
 aacattataa aaggaaaaca ttataaagta attaaatttt aaagccagta tgtgaaagaa 660  
 gagatggccc aaagtcttca ttaccctctt agagaagaaa ctccattaat gtgtgctcag 720  
 tctgggtcca ctccctagta accttaagca tagttacatt cactttttgt cttttacccc 780  
 cattttcagt tctgttgtga tcatctttta caacataatt caccctcaac tatttttgga 840  
 ggagtgtggg aaggaaataa acagtaacgt aaagtatata tgaaatcatg tttaaccttg 900  
 aagacaatga ccccttgatt tttactttcg gttaacaggt accacaacat cagagtatac 960  
 aagaatactg gaagtgtgtg aagaaagaaa gcattaaagg agtaaaagaa gtctggaaac 1020

60

aagctgaaaa aggtcttttt taataaaaga tataatagta tggcaattat attgttccaa 1080  
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tattctgtgt gaaataagca tgtcttgtac ttgctttctg attcataatt ttatgaaaga 1200  
acttagtaga aagaaaagta agtataaaaa tagatattgg attctgtcag aaggcctaga 1260  
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ttttatgtca gtagcttagc tgttttattgt ctttaaaata acatgtaaac ttcaatgttc 1560  
tatctggaag cagaataaaa tatttacata gatacaaaaa a 1601

<210> 43  
<211> 1344  
<212> DNA  
<213> Homo sapien

<400> 43  
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tccgcaaaga tggcggcggc tgcgggtagc tgcgcgcggg tggcggcctg gggcggaaaa 120  
ctgcgacggg ggctcgctgt cagccgacag gctgtgcgga gtcccggccc cttggcagcg 180  
gcagtggccg gcgcggccct ggccaggagca ggagcggcct ggcaccacag ccgcgtcagt 240  
gttgccggcg gggatggcag ttttacagtc tccgcacaga aaaatgttga acatggaata 300  
atatatattg ggaaaccgtc tcttcgtaag cagcgcttca tgcagtttct ttcactcgaa 360  
catgaaggag aatattatat gacaccacga gacttcctct tctcagtgat gtttgagcaa 420  
atggaacgta aaacttcagt caagaagctg acaaaaaagg acatcgagga tacactgtca 480  
gggatccaaa cagctggctg tggatcaact tttttcagag accttggcga taaagggcta 540  
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catgttgctt ttaaaatgct ggatacagat ggtaatgaga tgattgaaa aagggaattt 660  
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actggatatc aggaagcaat agtgaaagaa cctgaaatta acacaactct tcagatgcgt 780  
ttctttggaa aaagaggaca aagaaaactt cattataaag aatttcgaag atttatggaa 840  
aatttacaaa cagagattca agaaatggaa ttccttcagt tttctaaagg tttagatttc 900  
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atctattgga aaaatgtgag agagaagttg tcagcaggag agagcattag tttggatgaa 1020

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ttcaagtcac tttgccatct tacaacccac ttggaagact ttgctattgc catgcagatg 1080  
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 acaggacaag aactctcaaa caatatcttg gacactgtct ttaagatctt tgatttggat 1200  
 ggtgatgaat gtcttagtca tgaagagttt cttgggggtgt taaaaaacag aatgcacgca 1260  
 ggtttatggt cccccacatt ccaagggtcc gaaaactgga aggggtggag aaaggaacct 1320  
 ttaaggcgtg aagggtggaaa cctc 1344

<210> 44  
 <211> 1773  
 <212> DNA  
 <213> Homo sapien

<400> 44  
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 tccgcaaaga tggcgccggc tgcgggtagc tgcgcgcggg tggcggcctg gggcgaaaa 120  
 ctgcgacggg ggctcgctgt cagccgacag gctgtgcgga gtcccgccc cttggcagcg 180  
 gcagtggccg gcgcggccct ggcaggagca ggagcggcct ggcaccacag ccgcgtcagt 240  
 gttgcggcgc gggatggcag ttttacagtc tccgcacaga aaaatgttga acatggaata 300  
 atatatattg ggaaaccgct tcttcgtaag cagcgcttca tgcagtttct ttcactcgaa 360  
 catgaaggag aatattatat gacaccacga gacttcctct tctcagtcat gtttgagcaa 420  
 atggaacgta aaacttcagt caagaagctg acaaaaaagg acatcgagga tacactgtca 480  
 gggatccaaa cagctggctg tggatcaact tttttcagag accttggcga taaagggcta 540  
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 catgttgctt ttaaaatgct ggatacagat ggtaatgaga tgattgaaaa aagggaattt 660  
 ttttaagctgc agaagatcat aagtaacaa gatgacttga tgacagtga aactaatgaa 720  
 actggatatc aggaagcaat agtgaaagaa cctgaaatta acacaactct tcagatgcgt 780  
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 aatttacaaa cagagattca agaaatggaa ttccttcagt tttctaaagg tttgagtctc 900  
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 atttattgga aaaatgtgag agagaagttg tcagcaggag aggttggtat acccttttat 1020  
 tatgcatgtg ataaagatga aataataagt tagacatgtt tacataaagt aacttctgaa 1080  
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 atgctcttct cctgtaaagg aaaactactg cctaagacag aatcagtgtg gcaattacaa 1200  
 gttttccatt tccagtaaag tcaagaataa gacaagtatc actactgtta tttaatatca 1260

62

ctctgtaaat cttaaccagt ccaaattaac aagattatattt aaaagagtat aaaaatgtga 1320  
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 agaatccagt agaaaaaccg tagaaacaat aagaattcaa taaagtacct gtcacaatgc 1440  
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 ttactttctat tgtaagaaaa aaataaattg cagtagaaga acccagttat aactgcaaga 1740  
 taaatatata acaattagaa ataaatttaa caa 1773

<210> 45  
 <211> 756  
 <212> DNA  
 <213> Homo sapien

<400> 45  
 cgcgagagtt cccaagcggg aggcggcggc gccgggagag aagcgccgtc tagctgcgct 60  
 tccgcaaaga tggcggcggc tgcgggtagc tgcgcgcggg tggcggcctg gggcggaaaa 120  
 ctgcgacggg ggctcgctgt cagccgacag gctgtgcgga gtcccggccc cttggcagcg 180  
 gcagtggcgg gcgcggccct ggcaggagca ggagcggcct ggcaccacag ccgcgtcagt 240  
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 catgaaggag aatattatat gacaccacga gacttcctct tctcagtgat gtttgagcaa 420  
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 gggatccaaa cagctggctg tggatcaact tttttcagag accttggcga taaagggcta 540  
 atttcatata ccgagtatct tttcttgctt acaatcctca cttaaacccca ttctggatgt 600  
 catgttgctt ttaaaatgct ggatacagat ggtaatgaga tgattgaaaa aagggaatgt 660  
 ttttaaggtaa gtggacgcta attattttag gtttatcata aaatacctgg atgtttgtgt 720  
 gataatttta catttccatt aaaatcaaaa ttgtat 756

<210> 46  
 <211> 1879  
 <212> DNA  
 <213> Homo sapien

<400> 46  
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 tgtgggaaca agaataaaag agaaaccagg attgactggg aagagacaca aagaaacttt 120

gtcaaaattg gctgatattt gtacatttta atatattgtat tttttcctga agagctgtaa	180
ataataattg ggaggggaac agggagcagg tagaggtata gaagagccag gaatagcaga	240
atactggtaa ttattgaaga ttaataatgt ttacatgggtg acttggtcgt agaattctgt	300
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aagcacaggg agaaatgtgt ggatattgaa ctgggcatta tatcatttga ttgtcaactt	420
taaaaataaa aggtaaaata aatataaagc tttttaactt ttttcccaa aataattaag	480
taggggaaag ggggggtattg aaaactggct gagagattta gagaactaga aataaaccac	540
ttgcctaaaa caaacgtaat agaaatagct aaattcaaaa taattaatac ggaattaatt	600
gcagcagttt tcaaactggtt aaatagccca gaaaaaatg gatagaggtt tgtctcctaa	660
ttgatttgaa tccatagttt gggattttgt ctacatctga ttcttttaaa atgctttctt	720
ttttaaattht gctttccata tgaggattga tacaattgat tctgaaaggc agctgcagaa	780
gatcataagt aaacaagatg acttgatgac agtgaaaact aatgaaaactg gatattcagga	840
agcaatagtg aaagaacctg aaattaacac aactcttcag atgcgtttct ttggaaaaag	900
aggacaaaga aaacttcatt ataaagaatt tcgaagattt atggaaaatt taaaaacaga	960
gattcaagaa atggaattcc ttcagttttc taaaggtttg agtttcatga gaaaagaaga	1020
ctttgcagag tggctacttt ttttactaa cactgaaaat aaagatattt attggaaaaa	1080
tgtgagagag aagttgtcag caggagaggt tggatatacc ttttattatg catgtgataa	1140
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accagtccaa attaacaaga ttatttataaa gagtataaaa atgtgaaagg gggtagtagt	1440
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agtgggtgagg tttcaagtga tttttacttt ttttctttat acctttatgt attgttccaa	1740
aaaaatgttt acaatggaca tgtattttat gtaacttttt aaaaagtac ttctattgta	1800
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ttagaaataa atttaacaa	1879

<210> 47  
 <211> 570  
 <212> DNA  
 <213> Homo sapien

<400> 47  
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 gtcaaaattg gctgatattt gtacatttta atatatgtat tttttcctga agagctgtaa 180  
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 tcattttact taagtttgaa attttctgta ataaaaattt gtaagagggt ccaggggaat 360  
 aagcacaggg agaaatgtgt ggatattgaa cttggcatta tatcatttga ttgtcaatta 420  
 tttcagattt ttctcatctg taccttatat ctcataaatt tattgcatat tttatgtcag 480  
 tagcttagct gtttattgtc tttaaaataa catgtaaact tcaatgttct atctggaagc 540  
 agaataaaat atttacatag atacaaaaaa 570

<210> 48  
 <211> 699  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (110)..(110)  
 <223> n=a,c,g or t

<220>  
 <221> misc\_feature  
 <222> (159)..(159)  
 <223> n=a,c,g or t

<220>  
 <221> misc\_feature  
 <222> (174)..(174)  
 <223> n=a,c,g or t

<400> 48  
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 aggacagctt ttgatccaca acggacagct tgttgatcna atttcggtag gtancaagcc 180  
 tttctatgac aggatgtcca tgtgctggga ctctcctagc tttcaggatc aaataaaaaa 240  
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 cctctgtcaa cttgactttc aggtcttcta tcagctccaa gagttctggg gattcctttc 420  
 gcaacatttt cagcttctct ttcactgaaa ctttagccaa atccttcacg acccggtgtct 480  
 cagcctcatc tacctgaggc actgctcgtg ccgaattcgg cacgagggct aaatgaagtt 540  
 aaaaacttat ttcagatttt tctcatctgt accttatatc tcataaattt attgcatatt 600  
 ttatgtcagt agcttagctg tttattgtct ttaaaataac atgtaaactt caatgttcta 660  
 tctggaagca gaataaaata tttacataga tacaaaaaa 699

<210> 49  
 <211> 1960  
 <212> DNA  
 <213> Homo sapien

<400> 49  
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 tccgcaaaga tggcggcggc tgcgggtagc tgcgcgcggg tggcggcctg gggcggaaaa 120  
 ctgcgacggg ggctcgtgt cagccgacag gctgtgcgga gtcccggccc cttggcagcg 180  
 gcagtggccg gcgcggccct ggcaggagca ggagcggcct ggcaccacag ccgcgtcagt 240  
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<211> 1220

<212> DNA

<213> Homo sapien

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68

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 <213> Homo sapien

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70

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71

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<210> 57  
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 <212> DNA  
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72

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&lt;213&gt; Homo sapien

&lt;400&gt; 60

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&lt;210&gt; 61

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&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 61

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75

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&lt;213&gt; Homo sapien

&lt;400&gt; 68

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&lt;211&gt; 290

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 69

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&lt;210&gt; 70

&lt;211&gt; 565

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 70

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80

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&lt;211&gt; 7161

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 83

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&lt;211&gt; 7144

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 84

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&lt;211&gt; 1921

&lt;212&gt; DNA

&lt;213&gt; Homo sapien



114

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115

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 <212> DNA  
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&lt;211&gt; 8200

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 87

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129

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131

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132

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134

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159

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160

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161

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&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 104

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&lt;210&gt; 105

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 105

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162

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163

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&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 108

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164

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&lt;211&gt; 588

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 109

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165

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166

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167

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 <213> Homo sapien

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 ggtcaaacc ttcatctgca ccatgccc atgcggtggat gacggctgga accagattca 540  
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 <211> 510  
 <212> DNA  
 <213> Homo sapien

<400> 113  
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168

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cagactattt caccctacat ccttttaag tgcttgagat atgcatattt agtaggcata	420
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 <211> 752  
 <212> DNA  
 <213> Homo sapien

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tccccagaaa aggataatta taaaagacac caggaagcct cttttcaacc ttgttaaata	180
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 <211> 751  
 <212> DNA  
 <213> Homo sapien

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169

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 tcataaaggc ccaaaatgcg tcttgaaggg agtttttgca atacaaatcc taatcttaat 300  
 tatataaact ctattcttaa ctatcttaaa atacattaca aaagaccatt ctcaactttc 360  
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 acggctcatt aaatcttgaa tcattaagtc aagtaccttg gacaaatcat tttaaattaa 480  
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 aaagccacag aaaagctacg gaaataatgg aatgaacaca cagtgatatt tgcttcagga 600  
 acagactatt tcacctaca tccttttaaa gtgcttgaga tatgcatatt tagtaggcat 660  
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 caatgaaaca ttttcaaat gcaggtagca g 751

<210> 116  
 <211> 428  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (321)..(321)  
 <223> n=a,c,g or t

<400> 116  
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 tcagatgaga ctttaatacat tctacacaac ttatcaaaag cctactagat aaagctacgg 180  
 aaataatggg aatgatacac acagtgtata tttgcttcag ggacagacta tttcaccctt 240  
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 cttcattttc tatatatata naatataggg ctagacttcc ccgcaggctt ggcgatatgt 360  
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 tctctagc 428

<210> 117  
 <211> 671  
 <212> DNA  
 <213> Homo sapien

<400> 117  
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170

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acccaaaagt tcagtgtgtt ctcattaagt taccagaaat tacagatgtg aagatactcc 180
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gcttaaatac taaatagaga aaatctgcat attgacaaca taggtaattt aagactgggt 360
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tcttatagtg ttgcatccat ttaacatttt cccagaatac attcaggttt ttttaatccc 600
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<210> 118
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<212> DNA
<213> Homo sapien

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acccaaaagt tcagtgtgtt ctcattaagt taccagaaat tacagatgtg aagatactcc 180
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cctcagtctt ttattttat 679

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<210> 119
<211> 603
<212> DNA
<213> Homo sapien

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<400> 119
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171

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gtg							603

<210> 120  
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 <212> DNA  
 <213> Homo sapien

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caaaaggcag	ttttgggaaa	tattactagt
tagctcttca		120
ggtgtttact	tgtttaaagc	tcttttagttg
tttagaagca	tctgacttaa	cggagtagag
		180
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cctgggcgac	agagcgaaaa	aaaaaaaaaa
		240
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tccgtccttg	gaatcctaag	aaaattttcc
		300
agccgtatta	cccttctatg	aagcccacct
gtcaaccaac	aagcaccac	tcgatcagag
		360
cttccccagg	ctttttggtg	tctcctcctt
gcatgggaat	tgacttccaa	ggaccaccag
		420
acactgagga	agtattttta	catataaagc
aaaagcaaca	atagggcagc	tggagaaagg
		480
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ttagaaaaac	actcaaaaaa	tggtataataa
		540
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catctattta	aataaaaaa	ggaatcaata
		600
aaagtgaaaa	aaaaaa	
		616

<210> 121  
 <211> 611  
 <212> DNA  
 <213> Homo sapien

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tccttgcttg	agtcacacgg	gcagagcctg
		120
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gaagtagaag	gaggaccgaa	tggagaatg
		180

172

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 caagatgggt g 611

<210> 122  
 <211> 771  
 <212> DNA  
 <213> Homo sapien

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173

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&lt;210&gt; 124

&lt;211&gt; 1785

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 124

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174

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&lt;210&gt; 125

&lt;211&gt; 2416

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 125

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175

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176

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<212> DNA

<213> Homo sapien

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181

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&lt;213&gt; Homo sapien

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182

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gcattgacca ggccatccag acagagagcg gggatggctt gtctcccagg gcagtgggtg	2880
cacgtgccag cctagagggt tcggtttacc tgcattgcacc acggtccctt gagaatctgt	2940
gcccttcccc tcctggtagg ggatgcttgg aaagggtcaa tctgaggccc ttgctttcat	3000

184

gaaaggcctt gagggccaca gccaggttc tagaaatcta gaattgacct tggtttccag 3060  
 aatgaccagt ttgcatttcc tttatctgca caaagaagcg gatttcttgg gggctctctg 3120  
 ggtgtgagcg tagtgagtgt gaatgcatca aggtgcctaa aaatacaagg acagatgcca 3180  
 aatataagca tttttacctt gaagctgcct tgaattgagt ttgcaggaa aagtgtatta 3240  
 aaataattct taaaaactaa aaaaaaaaaa aaaaaaagat ctttaatata agcggac 3297

<210> 137  
 <211> 814  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (182)..(267)  
 <223> n=a,c,g or t

<400> 137  
 gtgggaggca ggagtgggct gtgtcacatc ggagcatggt gctgctactg gggtgactcg 60  
 tggaaggtta caccatgcaa tgggggtttc gctgcctttg cctgtccacc ccaaagtact 120  
 cctaacattg gaaagaagtg agttgagtgt acatttaaaa aatactattc taggctgggc 180  
 annnnnnnnnn nnnnnnnnnnn nnnnnnnnnnn nnnnnnnnnnn nnnnnnnnnnn nnnnnnnnnnn 240  
 nnnnnnnnnnn nnnnnnnnnnn nnnnnnnncta ctcttgtagg cagctgtgaa ctcgatggac 300  
 atttattctt accaaatggg gatgttacag cttctctaag acgtggctcc accaccggga 360  
 gtccgagtgc tgccaagagg aggtctctac tcggaacgca ggtgccgtct ttacagtgga 420  
 gccccaggaa gccgtgcagg tttgaggctc acctgagaag gcggcagtgct tgtgttccta 480  
 cctcagggtt cactgcaaac aatgcatacg ctgtagcagt tgccagcttg gtttgtcagt 540  
 gctggctctcc gtgattgggt ctcagggtgt agttgtagca aagttgcgtg ttaatcagag 600  
 agcgtcctgc ccatcccagg gtctcagcag ggctgaggca gcgtttgggg accagatccg 660  
 tgctgctcct tggcgatgtg caccacagtc atgggaccag agctaggccc actgtggggc 720  
 gagtggacac tcagctgggg gtcccattta tgggacacta aaaaactcag cagtgaacac 780  
 gacgttttaa cacggtatgt caagaaatca aaat 814

<210> 138  
 <211> 534  
 <212> DNA  
 <213> Homo sapien

<400> 138  
 ctgcattaat tttgatttct tgacataacc tgtaaaccg tcgtgttcac tgctgagttt 60  
 tttagtgtcc cataaatggg acccccagct gagtgtccac tcgcccaca gtgggcctag 120

185

```

ctctgggtccc atgactgtgg tgcacatcgc caaggagcag cacggatctg gtccccaac 180
gctgcctcag ccctgctgag accctgggat gggcaggacg ctctctgatt aacacgcaac 240
tttgctacaa ctcacacctg agaaccaatc acggagacca gcactgacaa accaagctgg 300
caactgctac agcgtatgca ttgtttgcag tgaaccctga ggtaggaaca cagcactgcc 360
gccttctcag gtgagcctca aacctgcacg gcttcctggg gctccactgt aaagacggca 420
cctgcgttcc gagtagagac ctctcttggg cagcactcgg actcccgggtg gtggagccac 480
gtcttagaga agctgtaaca tcaccatttg gtaagaataa atgtccatcg agtt 534

```

```

<210> 139
<211> 410
<212> DNA
<213> Homo sapien

```

```

<400> 139
gtaaccctct aggagactag aggagctaca gtgttatgtt ctgggtgggt ggaatgactg 60
agacacctga gctatgtcac attcagaaat cttaattagt ttgcagagag caagaaagaa 120
attgcctact ctgcatccca tcttctctgt ttgtgtaaag agcccagtaa aacaagacat 180
agcagctcaa ttcagaaatg tgaagcatgt aaccatgata caagagttac ctatatgatt 240
ttcaacaaaa gaaaacttgg atatatattgg gagctgtgag gccaaagtcac aataatacat 300
tagaaataaa ttttaatactg tatagttttt aaagtgttga aatatgagtc ccacaggaaa 360
aggaaaatat aaaagataat aaattagatc aaaaagctgt tacgggggaga 410

```

```

<210> 140
<211> 419
<212> DNA
<213> Homo sapien

```

```

<400> 140
gtaaccctct aggagactag aggagctaca gtgttatgtt ctgggtgggt ggaatgactg 60
agacacctga gctatgtcac attcagaaat cttaattagt ttgcagagag caagaaagaa 120
attgcctact ctgcatccca tcttctctgt ttgtgtaaag agcccagtaa aacaagacat 180
agcagctcaa ttcagaaatg tgaagcatgt aaccatgata caagagttac ctatatgatt 240
ttcaacaaaa gaaaacttgg catatcattt gggcagctgt gaggcccaag tcatcaataa 300
tacattagca aataaattta atactgtatc agttttttaa gtgttgaaat atgagtcacca 360
caggataaag gaaatatata aaagataata aattagatca aaaagctgtt acgggggaga 419

```

```

<210> 141
<211> 411
<212> DNA

```



186

&lt;213&gt; Homo sapien

&lt;400&gt; 141

```

gtaaccctct aggagactag aggagctaca gtgttatgtt ctgggtgggt ggaatgactg      60
agacacctga gctatgtcac attcagaaat cttaattagt ttgcagagag caagaaagaa      120
attgcctact ctgcatocca tcttctctgt ttgtgtaaag agcccagtaa aacaagacat      180
agcagctcaa ttcagaaatg tgaagcatgt aaccatgata caagagttac ctatatgatt      240
ttcaacaaaa gaaaacttgg atatatttgg gagctgtgag gccaaagtcac aataatacat      300
tagaaataaa ttttaatactg tatagttttt aaagtgttga aatatgagtc ccacaggaaa      360
aggaaaatat aaaagataat aaattagatc aaaaagctgt tacggggaag a              411

```

&lt;210&gt; 142

&lt;211&gt; 367

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 142

```

cagaaagctt aatgtaaagg tggctgatac tgctgtttcc ttagacactg acaccaaata      60
caataaagaa gtctctcaag aggaaaacat ggtgtgttta caggagcaac taacagttgg      120
tttgtaggca tcttaaattg tggatggcaa gcttgggttt cccaaagggt tctagtcttt      180
atacgtcttc tagtaggtgc ccaggtagt atggcctgtg ttaccagagt aacaatgaaa      240
atggctacgt ctttaaatca ggccacttta cagtgaacta tggtccttaa ttgctatcac      300
atttcaaaca agaactatga ccaattaaac ttactattg ttgaactgcc aaaaaaaaaa      360
aaaaggg                                           367

```

&lt;210&gt; 143

&lt;211&gt; 711

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 143

```

ataaacgagg tagatgttac agttaatgga acatcatgca gottcatatc tcctttttac      60
tcaagctggg gcctatgttt ggtattgaac aaaatggaat gctgcaattt tctctctact      120
gattttgtta ctacagaaag cttaatgtaa aggtggctga tactgctgtt tccttagaca      180
ctgacaccaa atacaataaa gaagtctctc aagaggaaaa catggtgtgt ttacaggagc      240
aactaacagt tggttttag gcatcctaaa tggatggatgg caagcttggg tttcccaaag      300
gtttctagtc ttatacgtc ttctagtagg tgcccagggt agtatggcct gtgttaccag      360
agtaacaatg aaaatggcta cgtctttaa tcaggccact ttacagtga ctatggctct      420
taattgctat cacatttcaa acaagaacta tgaccaatta aactttacta ttgttgaact      480

```

187

gcctcaagtt ccagaagttt ggtttgtttg atttagattg gtctgtatgg gctcttggtta 540  
 aggagtgtac ttggtcttt tgataccatt ctcttggttag tgatcacagt cgtctctctg 600  
 ggtgtgttgt accctctcaa gtcttaaata ttgtatgca gccattcatt gagcatcaaa 660  
 cggtttcatt ttgactagat tagcaagaat ataaaaaatt atcaactgat g 711

<210> 144  
 <211> 483  
 <212> DNA  
 <213> Homo sapien

<400> 144  
 ataaacgagg tagatgttac agttaatgga acatcatgca gcttcatatc tcctttttac 60  
 tcaagctggg gcctatgttt ggtattgaac aaaatggaat gctgcaattt tctctctact 120  
 gattttgtta ctacagaaag cttaatgtaa aggtggctga tactgctgtt tccttagaca 180  
 ctgacaccaa atacaataaa gaagtctctc aagaggaaaa catgggtgtgt ttacaggagc 240  
 aactaacagt tggttttag gcatcctaaa tgggtggatgg caagcttggg tttcccaaag 300  
 gtttctagtc tttatacgtc ttctagtagg tgcccaggtt agtatggcct gtgttaccag 360  
 agtaacaatg aaaatggcta cgtcttttaa tcaggccact ttacagtga ctatggctct 420  
 taattgctat cacatttcaa acaagaacta tgaccaatta aactttacta ttgttgaact 480  
 gcc 483

<210> 145  
 <211> 359  
 <212> DNA  
 <213> Homo sapien

<400> 145  
 cggaaaaaaa agaactagtt taaattctga ctgtatcact gaaaggctgt gtagctgtgt 60  
 gaccgtaagc aagtcactta actccagatt ctcatgtctg tcatctataa acagggatga 120  
 atgaatatac acctcagagt tgtaagaat ccaatgagaa aatcacgggt aaccttata 180  
 taaatgggtg tgaaacattt caaagataca agcatccttg gcctttgcag ccagaatca 240  
 tccctccaca ttttctctac aatccaacca catcaagaaa tgataactgc tcagaaagtt 300  
 tatcaatatt taccaaaact catggattta aaataaacat taagtttcta ccataaaaa 359

<210> 146  
 <211> 1122  
 <212> DNA  
 <213> Homo sapien

<400> 146  
 aaaataaaca ctggccaggc acaggggctc acacctgtaa tcccagcatt ttggggaggcc 60

188

```

aaggcaggag gatcacttga gcccaggcgt ttaagaccag cctgggcaac atagggagac 120
ccgtttctac aaaaaaagaa aaaattagct gggcttggtg gtacacgcct gtagtcccag 180
ctgcacagga ggctgaggtg ggaggaaggc ttgaggccag gagttcaaga tcagcctggt 240
caacatagca agaccccatc tctacaaaaa agaaaaaaat tagcaaggca tggtagcatg 300
tgcctgtagt ccctgctact caggaggctg aggcaggagg atcacttgag cccaggagtt 360
caaggctgca gtgagccata atcctgcact gtagcctggg tgacagagtg agtcccccat 420
ctcggaaaaa aaagaactag tttaaattct gactgtatca ctgaaaggct gtgtagctgt 480
gtgaccgtaa gcaagtcact taactccaga ttctcagtgc tgtcatctat aaacagggat 540
gaatgaatat acacctcaga gttgttaaga atccaatgag aaaatcacgg gtaaccctta 600
tataaatggt tgtgaaacat ttcaaagata caagcatcct tggcctttgc agcccagaat 660
catccctcca catttttctt acaatccaac cacatcaaga aatgataact gctcagaaag 720
tttatcaata tttaacaaaa ctcatggatt taaaataaac attaagtttc tacaataagc 780
attcttgtaa ttctatgcca tttgtactcc cttgatcttc accctatttg gcaatatcaa 840
cttttttttt ttgagatgga gtctcacttt gtcaccagg ctggagtgcg gtggtgcaat 900
ctcggctcac tgcaacctcc gcctcccagg ttcaagcaat tctcgtgcct cagcctccca 960
agtagctggg attacaggca cgcaccacca cgtcttgcta atttttgtat ttttagtaga 1020
gatgggtttt taccatgatg gtcaggctgg tcttgaactc ctgacctcag gtgatccacc 1080
cacctcggcc tcccaaagtg ctgggattac aggcgtgagc ca 1122

```

<210> 147  
 <211> 283  
 <212> DNA  
 <213> Homo sapien

```

<400> 147
cctagtttct gccactcctg ctgttaaact ttttttttta aaagtttagt agttcacata 60
tgtaaactat taatgcagaa tgaactgctc atttcttctt ccctgagtta cctccatgag 120
acaaatccta gtgtgggatg tcccggaaact accatgcacc tttgccccac cgagtttccc 180
aagaattggt gaaagccttt gctgcagtgg tctgagcagg tgtgctgttg ctgctgcaaa 240
acataccttc atagctgaac tgcttaggaa gccagcagag aag 283

```

<210> 148  
 <211> 371  
 <212> DNA  
 <213> Homo sapien

```

<400> 148
cctagtttct gccactcctg ctgttaaact ttttttttta aaagtttagt agttcacata 60

```

189

tgtaaaactat taatgcagaa tgaactgctc atttcttcct ccctgagtta cctccatgag 120  
 acaaatccta gtgtgggatg tcccggaact accatgcacc ttgccccac cgagtttccc 180  
 aagaattggt gaaagccttt gctgcagtgg tctgagcagg tgtgctgttg ctgctgcaaa 240  
 acataccttc atagctgaac tgcttaggaa gccagcagag aagttttttc ctcccttcct 300  
 tccttccttc ctcccttcct tccttcccc ctctccattc cattgtaatt aaagtggcct 360  
 agctaagtgc a 371

<210> 149  
 <211> 217  
 <212> DNA  
 <213> Homo sapien

<400> 149  
 cctagtttct gccactcctg ctgttaaact ttttttttta aaagtttagt agttcacata 60  
 tgtaaaactat taatgcagaa tgaactgctc atttcttcct ccctgagtta cctccatgag 120  
 acaaatccta gtgtgggatg tcccggaact accatgcacc ttgccccac cgagtttccc 180  
 aagaattggt gaaagccttt gctgcagtgg tctgagc 217

<210> 150  
 <211> 879  
 <212> DNA  
 <213> Homo sapien

<400> 150  
 gaaaatgttc ccttctgtag aaactttatt aatcccttat gatcttaata ctgttaataa 60  
 tggactagac tgtaaaggat taggtaactg aggtgttcaa tatggatact tgttttatgt 120  
 ttaatcaaat ttatctgact ctaaataaat ttggctgaaa ctagacagat tccttttcta 180  
 ttgagacagt gggctctatt aagcactatg tctgcatagg aaacattaca attaatattg 240  
 cagtgacaat atgcttttta actaacagac taatggaagg aggactgatg taaagcataa 300  
 ttctcaaaaa gaggggggta aaaccttggg ttctactaca attattcatt ttatagtatt 360  
 gtttgataac acatacttta ttaaattgta gatgcattgt aagtttttat agtatatggg 420  
 aatctaaata aaaggagtta ttgggtgtt atgccatatt tagcataaat attaccatcc 480  
 atgtatgttg ttgacttaaa aactgttat tttctaaaat gtaagcatag aaaaagaata 540  
 aaattcttag ttgatattgc agaaatatat tgtagtgtt gcagcatgaa aaggttttat 600  
 atataataat atacacttaa taattaattt ccaaaggctg cctgtgggtca gccttcttg 660  
 aaagcatgga ttctggcaaa tgagcaatat aatctcttta agaccattta agctcttaat 720  
 ctcttcaaac cagtaccaa gtctgttcat ttgtgtgtaa tagttattgt gtattgttc 780

190

tttttaattg tgtaagtgag attcaacatc acttgtcaga taagaaaaaa aaccttcaaa 840  
 ataaacgtta atttttccca ttattgctag aaggaactt 879

<210> 151  
 <211> 879  
 <212> DNA  
 <213> Homo sapien

<400> 151  
 gaaaatgttc cttctgtag aaactttatt aatcccttat gatcttaata ctgttaataa 60  
 tggactagac tgtaaaggat taggtaactg aggtgttcaa tatggatact tgttttatgt 120  
 ttaatcaaat ttatctgact ctaaataaat ttggctgaaa ctagacagat tccttttcta 180  
 ttgagacagt gggctctatt aagcactatg tctgcatagg aacattaca attaattttg 240  
 cagtgacaat atgcttttta actaacagac taatggaagg aggactgatg taaagcataa 300  
 ttctcaaaaa gaggggggta aaaccttggg ttctactaca attattcatt ttatagtatt 360  
 gtttgataac acatacttta ttaaattgta gatgcattgt aagtttttat agtatatggg 420  
 aatctaaata aaaggagtta ttgggttgtt atgccatatt tagcataaat attaccatcc 480  
 atgtatgttg ttgacttaaa aactgttat tttctaaaat gtaagcatag aaaaagaata 540  
 aaattcttag ttgatattgc agaaatatat tgtagtgtt gcagcatgaa aaggttttat 600  
 atataataat atacacttaa taattaattt ccaaaggctg cctgtggtca gccttctttg 660  
 aaagcatgga ttctggcaaa tgagcaatat aatctcttta agaccattta agctcttaat 720  
 ctcttcaaac cagtaccaa gtctgttcat tttgttgtaa tagttattgt gtattgtttc 780  
 tttttaattg tgtaagtgag attcaacatc acttgtcaga taagaaaaaa aaccttcaaa 840  
 ataaacgtta atttttccca ttattgctag aaggaactt 879

<210> 152  
 <211> 360  
 <212> DNA  
 <213> Homo sapien

<400> 152  
 ggtattgatt tgagtattat tagtaattaa tctccttgtc taggtttctt cacatacaaa 60  
 tttccaagta ttgttcaaag gaagtctgta agatttaggc cattgtttta caaaatacaa 120  
 atatttggct tggtgagaat gtcttcctat agataactaa gaaactttta gacttgtgga 180  
 tgttctttta attactgtct aatgaatgca cagtaaaatc aaagatcaac caagtatagc 240  
 aaattgcagc agcatatttt agaaaggatg ttatataaga agcaaggata cctgaatcct 300  
 agtcttggct tcaatagtta ctagctccag acacaggata cagtgttaact ttgggtgatt 360

191

<210> 153  
 <211> 360  
 <212> DNA  
 <213> Homo sapien

<400> 153  
 ggtattgatt tgagtattat tagtaattaa tctccttgct taggtttctt cacatacaaa 60  
 tttccaagta ttgttcaaag gaagtctgta agatttaggc cattgtttta caaaatacaa 120  
 atatttggtc ttgttgagaat gtcttcctat agataactaa gaaactttta gacttggtga 180  
 tgttctttta attactgtct aatgaatgca cagtaaaatc aaagatcaac caagtatagc 240  
 aaattgcagc agcatatttt agaaaggatg ttatataaga agcaaggata cctgaatcct 300  
 agtcttggtc tcaatagtta ctatgtccag acacaggata cagtgttaact ttgggtgatt 360

<210> 154  
 <211> 150  
 <212> DNA  
 <213> Homo sapien

<400> 154  
 gattgggttg ttcgggtgag ctctgaaagc cctaaaaaga aaaagggtgct gggttttcagg 60  
 gtacttgagt aagctgtcat ctctagtcaa aaaagggccca cttggatcta ttttaaattt 120  
 agggccagtg gccgggcacg gtggctcact 150

<210> 155  
 <211> 150  
 <212> DNA  
 <213> Homo sapien

<400> 155  
 gattgggttg ttcgggtgag ctctgaaagc cctaaaaaga aaaagggtgct gggttttcagg 60  
 gtacttgagt aagctgtcat ctctaggcaa aaaagggccca cttggatcta ttttaaattt 120  
 agggccagtg gccgggcacg gtggctcact 150

<210> 156  
 <211> 129  
 <212> DNA  
 <213> Homo sapien

<400> 156  
 gattgggttg ttcgggtgag ctctgaaagc cctaaaaaga aaaagggtgct gggttttcagg 60  
 gtacttgagt aagctgtcat ctctagtcaa aaaagggccca cttggatcta ttttaaattt 120  
 agggccagt 129

<210> 157  
 <211> 612  
 <212> DNA

192

&lt;213&gt; Homo sapien

&lt;400&gt; 157

tgccccagcc tgctgtgtga ccttagtcat gtagcttacc ctctctgggc aacttttctt	60
tctccatcta taaaatgaag gggtttagact gggccaacac tgagcctccc cctgagtctg	120
agtctttgtt gtctgtagat ctgcctgatt tgggggtggct ctgctgggtac tcccacttcc	180
tgctccatat ctacctcccc ttgggtatccc acattgtctc ctgcatgtct tgttgcccca	240
gggccctgac tgggtactcct ataattaact cctgcccattg ctcaggacat ggagggcctg	300
cttggtcttg ccagaccag tggcctgttg gggcccgggc cccaccctca cggactggcc	360
agcgttccca accccagggc cagggcaagg cgtctgctcc cacagtggct acctccagcc	420
ggcccagcac attcctcagg cttatctgga ggcccgcccc actggactct gccctccac	480
ccaggaagca gcaccagag ctgcgtgcgg aagagttgca gggcctggga acaggccctg	540
cgtgagctcg aggtagtgat tcttagcctg gggctggaga gaaacaggta gaggaccggg	600
tggggcagga gg	612

&lt;210&gt; 158

&lt;211&gt; 614

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 158

tgccccaggg ctgctgtgtg accttagtca tgtagcttac cctctctggg caacttttct	60
ttctccatct ataaaatgaa ggggttagac tgggtcaaca ctgagcctcc ccctgagtct	120
gagtctttgt tgtctgtaga tctgcctgat ttgggggtggc tctgctggta ctcccacttc	180
ctgctccata tctacctccc cttgggtatcc cacattgtct cctgcatgtc ttgttgcccc	240
agggccctga ctggtactcc tataattaac tcctgcccatt gctcaggaca tggagggcct	300
gcttggtctg gccagaccca gtggcctgtt. gggggccggg cccaccctc acggactggc	360
cagcgttccc aacccaggg ccagggcaag gcgtctgctc ccacagtggc tacctccagc	420
cggcccagca cattcctcag gcttatctgg agggccgccc cactggactc tgccctccca	480
cccaggaagc agcaccaga gctgcgtgcg gaagagttgc agggcctggg aacaggccct	540
gcgtgagctc gaggtagtga ttcttagcct ggggctggag agaaacaggt agaggaccgg	600
gtggggcagg aggg	614

&lt;210&gt; 159

&lt;211&gt; 258

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 159

193

```

gtgagattga aagtcagcaa atgcaaactc attttattgg aagcgggtga gaggccgtga      60
gcggtggttag taacaggatg aataaactca gcctctgcct tcttcctgta gctgggacag     120
ccatgaaagc ctccagtcca aatgcaaagg caagtgggta ggacaggcct tctgtggtcc     180
tcagtcagcc tccttccttg gccactcctg ccattgtgca gtggactcct gggcagaggg     240
cttctcagta aggcagga                                     258

```

```

<210> 160
<211> 259
<212> DNA
<213> Homo sapien

```

```

<400> 160
gtgagattga aagtcagcaa atgcaaactc attttattgg aagcgggtga gatgccgtga      60
gcggtggttag taacaggatg aataaactca gcctctgcct tcttcctgta gctgggacag     120
ccatgaaagc ctccagtcca aatgcaaagg caagtgggta ggacaggcct tctgtggtcc     180
tcagtcagcc tccttccttg gccactcctg ccattgtgca gtggactcct gggcagaggg     240
cttctcagta aggcaggag                                     259

```

```

<210> 161
<211> 148
<212> DNA
<213> Homo sapien

```

```

<400> 161
ggttgagatg ccgtgagcgg tggtagtaac aggatagaat caacattcag acctctgact      60
tcttcctgta gctgggacag accatgacag cctccagtcc aaatgcaaag tggcaagtgg     120
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<210> 162
<211> 337
<212> DNA
<213> Homo sapien

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<400> 162
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ctttcagagt cttcacaaac aggaactgct ttccttctca gaaaaaatg ctgctaagtt     120
gaagatggaa ctgaggcagg ctccaggaa cctaactaaa tacaaaactg aatgaactat     180
tgtggtaaat gggagcaggc gctcttcatt ttatgagata gatgaattac tgaaaaaat     240
acacagacat ggagtttctt ggggaagtca attaaaaaca aaatcccagt actgtagtag     300
ttggtcattt aaaagaaaat tgttggccgg gcgcggg                                     337

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<210> 163

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194

<211> 337  
 <212> DNA  
 <213> Homo sapien

<400> 163  
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 ctttcagagt cttcacaaac aggaactgct ttcccttctca gaaaaaatg ctgctaagtt 120  
 gaagatggaa ctgaggcagg ctccaggaac cctaactaaa taaaaactg aatgaactat 180  
 tgtggtaaata gggagcaggc gctcttcatt ttatgagata gatgaattac tgaaaaaat 240  
 acacagacat ggagtttctt ggggaagtca attaaaaaca aaatcccagt actgtagtag 300  
 ttggtcattt aaaagaaaat tgttgccgg gcgcggg 337

<210> 164  
 <211> 720  
 <212> DNA  
 <213> Homo sapien

<400> 164  
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 cctgtctctc tgtggtagac ccacagcact cttcagatgc ccaactgggtcc cctggccttt 180  
 actttctagt ctaggagact gaggtctaaa ggaaagaaat ggctgcctg cagccatcca 240  
 cggaagatgc aaaagagacc acaaatagag tccagggtgcc tgggccctct tttgccccaa 300  
 ggcctcctcc ccacagaagg tcccatggat cacttcccct tgaacgccag cactaggact 360  
 gcctgggtag ctgatataga tggagacgca caatcctctt ggcccagatg gggaactgag 420  
 ccgcaagcag tggctcggca gccactaagg ccgaggttta gaaaagtacc actcttgcca 480  
 agaaggaatg tgagggaaaag gccaggaggc tgggcgatgc tgggtggtgtg actttgagct 540  
 ggcgtcgtgg tttgtggcgt cctcagacca agcagcgga gcacggcaca aaggttgggg 600  
 catggcttct tcacaccag ctctccact cacatgtgct gcaaccccg gcaagccgct 660  
 tgctccctg aacctcagtt ttctcatcca taaaatgagg tttaggatca taagactgcc 720

<210> 165  
 <211> 800  
 <212> DNA  
 <213> Homo sapien

<400> 165  
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 cctgtctctc tgtggtagac ccacagcact cttcagatgc ccaactgggtcc cctggccttt 180

195

actttctagt ctaggagact gaggtctaaa ggaaagaaat ggcctgcctg cagccatcca	240
cggaagatgc aaaagagacc acaaatagag tccaggtgcc tgggcectct tttgccccaa	300
ggcctcctcc ccacagaagg tcccatggat cacttcccct tgaacgccag cactaggact	360
gcctgggtag ctgatataga tggagacgca caatcctctt ggcccagatg gggaaactgag	420
ccgcaagcag tggctcggca gccactaagg ccgaggttta gaaaagtacc actcttgcca	480
agaaggaatg tgagggaaag gccaggagggc tgggcgatgc tgggtggtgtg actttgagct	540
ggcgtcgtgg tttgtggcgt cctcagacca agcagcggca gcacggcaca aaggttgggg	600
catggcttct tcacaccag ctctccact cacatgtgct gcaaccccg gcaagccgct	660
tgctccctg aacctcagtt ttctcatcca taaaatgagg tttaggatca taagactgcc	720
ttggctgggc gtagtggctc acgcctgtaa tcccagccat tcgggagttt gaggcaggag	780
aatggcgtga acccgggagg	800

<210> 166  
 <211> 781  
 <212> DNA  
 <213> Homo sapien

<400> 166	
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cccacagcac tcttcagatg ccactggtc ccctggcctt tactttctag tctaggagac	180
tgaggctcaa aggaaagaaa tggcctgcct gcagccatcc acggaagatg caaaagagac	240
cacaaataga gtccaggtgc ctggggccctc ttttgcccca aggcctcctc cccacagaag	300
gtcccatgga tcacttcccc ttgaacgcca gcactaggac tgcctgggta gctgatatag	360
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agccactaag gccgaggttt agaaaagtac cactcttgcc aagaaggaat gtgagggaaa	480
ggccaggagg ctgggcgatg ctggtggtgt gactttgagc tggcgtcgtg gtttgtggcg	540
tcctcagacc aagcagcggc agcacggcac aaaggttggg gcatggcttc ttcacaccca	600
gctcctccac tcacatgtgc tgcaaccccg ggcaagccgc ttgcctccct gaacctcagt	660
tttctcatcc ataaaatgag gtttaggatc ataagactgc cttggctggg cgtagtggct	720
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g	781

<210> 167  
 <211> 1095  
 <212> DNA

196

&lt;213&gt; Homo sapien

&lt;400&gt; 167

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gtctttggat agtcagccac' atctatggtc tccaagggcc' ctttctcatc gccgctgcta	120
tgggagcctc aatgagagaa ccagggattc tgtacatcat gtagccctgg atctggcgct	180
ggtgctcogt ctctaaggcc cttgtcctgt ctcaggcagg ggctcacttc gacatcgctc	240
cctccctcat ttcttgccctg ctacagccaa gggagccaat gatctcccg agcaaaaact	300
cagcctcccg ctgcttttcc ctcaattgaag caggtgtaaa ttaggaggaa atggatctgt	360
ctaagttttt ggtccaaccc caataaaaag ctcatccaac tgttgtttat gagccccaag	420
cctggagggga gaggccgtga tttctaatta ctgaacaatg agcctttgat cagactaata	480
aagagtcatt tccaagttat gtagttgggc tcccagggac tgggagtcag aagactcggt	540
tgataatttt ttttattgtg ttaatgagca gatggatgga gcttcaggct agcagataat	600
tcacagggaa taatcccatt taccctgtgt gtgacagaga tgtgttcaa gatgggacga	660
tgtgttgctc cccagctggt ggcagggtaa gctgtggctt caagccctct ctccctctcca	720
tttttgttca tttgtttgcc accatccatc cctatgaccg actggcaaag gacacaggct	780
tcattccagta ctagccatgt ggccttgga aggtcacttt cccctgggg tectcatcta	840
tgaaatgatg atgatgatta tagtagtcaa ttcctgggac tgctataatg actgcattgg	900
gtaatctatg tggaaggatt tatttagcca aatggggatt ccatatttat tggctgggtg	960
tgcttactaa gcacctccta tttgccaggc tttgggggtcc tcatggggag aaatacatgg	1020
agcatgggct ccattcctga tctgctttt aagagtgata ctccctctcc ctctccctct	1080
ccctctccct ctccc	1095

&lt;210&gt; 168

&lt;211&gt; 1423

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (246)..(328)

&lt;223&gt; n=a,c,g or t

&lt;400&gt; 168

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tgaagaatga agacatttct gctctcagct ccgggggtga ggtgtgcctg gcctctgcct	120
ccacctcct cctcttcacc aggtgcatgc atgccctctc tgagtctgga ctttcttcc	180
cctccaggag ggaccaccct ccctgactgg cctgggatat ctttacaagc aggcactgta	240

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cactgcctgc cctcttctga cctcaggggt ctttggatag tcagccacat ctatggtctc 420
caaggcccct ttctcatcgc cgctgctatg ggagcctcaa tgagagaacc agggattctg 480
tacatcatgt agccctggat ctggcgctgg tgctccgtct ctaaggcccct tgtcctgtct 540
caggcagggg ctacttcga catcgctccc tccctcattt cttgctgct acagccaagg 600
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catccaactg ttgtttatga gcccgaagcc tggagggaga ggccgtgatt tctaattact 780
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tggggtcctc atggggagaa atacatggag catgggctcc attcctgatc ctgcttttaa 1380
gagtgatact tcctctccct ctccctctcc ctctccctct ccc 1423

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<210> 169
<211> 1033
<212> DNA
<213> Homo sapien

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<400> 169
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tgctccgtct ctaaggcccct tgtcctgtct caggcagggg ctacttcga catcgctccc 180
tccctcattt cttgctgct acagccaagg gagccaatga tctcccgag caaaaactca 240
gcctcccgct gcttttccct cattgaagca ggtgtaaatt aggaggaaat ggatctgtct 300
aagtttttgg tccaacccca ataaaaagct catccaactg ttgtttatga gcccgaagcc 360
tggagggaga ggccgtgatt tctaattact gaacaatgag cctttgatca gactaataaa 420

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198

gagtcatttc caagttatgt agttgggctc ccagggactg ggagtcagaa gactcgtttg 480  
 ataatttttt ttattgtgtt aatgagcaga tggatggagc ttcaggctag cagataattc 540  
 acaggggaata atcccattta ccctgtgtgt gacagagatg tgttccaaga tgggacgatg 600  
 tgttgctgcc cagctgggtg cagggtaagc tgtggcttca agccctctct cctctccatt. 660  
 tttgttcatt tgtttgccac catccatccc tatgaccgac tggcaaagga cacaggcttc 720  
 atccagtact agccatgtgg ccttgggaag gtcactttcc ccctggggtc ctcatctatg 780  
 aaatgatgat gatgattata gtagtcaatt cctgggactg ctataatgac tgcattgggt 840  
 aatctatgtg gaaggattta tttagccaaa tggggattcc atatttattg gctgggtgtg 900  
 cttactaagc acctcctatt tgccaggctt tggggctctc atggggagaa atacatggag 960  
 catgggctcc attcctgac ctagcttttaa gagtgatact tcctctccct ctccctctcc 1020  
 ctctccctct ccc 1033

<210> 170  
 <211> 524  
 <212> DNA  
 <213> Homo sapien

<400> 170  
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 ggcattggaga aactcaaaact tcccatgttt ttccagtcaa ataataatcc atcccttgcc 180  
 atctcctgga ctctaaatgt ttcaaagtac aatatgaaaa agaaaaatct gagccaccac 240  
 gccagccaa ccccttggtg tattgacttg ctgagtgcac caggcaatgg ttgtggacac 300  
 aatgtggtct catgggagag ctctgtata caaggatatag taatgaggga gcgtctggtt 360  
 aacaggattg gcgttcacct tccttggcat tcctaattct tgtagtgaga catgtttttt 420  
 tttgagattt caagatacat aaaaatctcc tgggaaactt caaaattgag tcattttatt 480  
 ccgaaatacc cattgaggta gagctcctag tccttttgag aagc 524

<210> 171  
 <211> 524  
 <212> DNA  
 <213> Homo sapien

<400> 171  
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 tttgaagttt cccagggaga tttttatgta tcttgaaatc tcaaaaaaaaa acatgtctca 120  
 ctacaaagat taggaatgcc aaggaagggtg aacgccaatc ctgttaacca gacgtccct 180

199

cattactata ccttgatatac aggagctctc ccatgagacc acattgtgtc cacaaccatt 240  
gcctgatgca ctcagcaagt caatacacca aggggttggc tgggcgtggt ggctcagatt 300  
tttctttttc atattgtact ttgaaacatt tagagtccag ggagatggca agggatggat 360  
tattatttga ctggaaaaac atgggaagtt tgagtttctc catgcctact cctgttggt 420  
aattgtgttc catatcccaa ggatgaaatt tcaaacaaga aatagaatgc cttttgtttt 480  
ccttggagct tagcaagttg aagtcttcta agtcctgtga ggtc 524

&lt;210&gt; 172

&lt;211&gt; 934

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 172

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ctttcttggg cccctctgca cgtgggcagt ccttccatga tgacagctgc cctgttatgg 180  
tgggattact ttggaggggtg gatgtggccc aggggaagtgt gtactctcag tgggcaggcc 240  
ttctgttttg atcattttgt agccagcat ctaacacaag gtgctcgtga ctcaagacct 300  
tatgtaaaga gggagggatg aacacaagga agaaagttcc ccagaaatcc ttccttacac 360  
ctgaaccgat tccttcctat atgtcctcag cttgagtcac tttctgtagc tccctcttat 420  
ttccatcaga tacttgata cattttaaatt tgtatcccc aaatatcagt gagagaaatc 480  
acatccatga tctacactgc attgaccagg ccatccagac agagagcggg gatggcttgt 540  
ctcccagggc agtgggtgcca cgtgccagcc tagaggtttc ggtttacctg catgcaccac 600  
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tgaggccctt gctttcatga aaggccttga ggccacagc caggcttcta gaaatctaga 720  
attgaccctg gtttccagaa tgaccagttt gcatttcctt tatctgcaca aagaagcggg 780  
tttcttgggg gtcttctggg tgtgagcgta gtgagtgtga atgcatcaag gtgcctaaaa 840  
atacaaggac agatgccaaa tataagcatt ttaccttga agctgccttg aattgagttt 900  
cgcaggaaaa gtgtattaaa ataattctta aaaa 934

&lt;210&gt; 173

&lt;211&gt; 1129

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 173

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ggtaaaaatg cttatatattg gcatctgtcc ttgtattttt aggcaccttg atgcattcac 120

200

actcactacg ctcacacca gaagaccccc aagaaatccg cttctttgtg cagataaagg 180  
 aaatgcaaac tggtcattct ggaaaccagg gtcaattcta gatttctaga agcctggctg 240  
 tgggcctcaa ggcccttcat gaaagcaagg gcctcagatt gaccctttcc aagcatcccc 300  
 taccaggagg ggaagggcac agattctcaa gggaccgtgg tgcattgcagg taaaccgaaa 360  
 cctctaggct ggcacgtggc accactgccc tgggagacaa gccatccccg ctctctgtct 420  
 ggatggcctg gtcaatgcag tgtagatcat ggatgtgatt tctctcactg atatttgggg 480  
 gatacaattt aaaatgtatc caagtatctg atggaaataa gagggagcta cagaaaatga 540  
 ctcaagctga ggacatatag gaaggaatcg gttcagggtg aaggaaggat ttctggggaa 600  
 ctttcttctt tgtgttcac cctccctctt tacataaggt cttgagtcac gagcaccttg 660  
 tgttagatgc tgggctacaa aatgatcaaa acagaaggcc tgcccactga gagtacacac 720  
 ttccctgggc cacatccacc ctccaaagta atcccaccat aacagggcag ctgtcatcat 780  
 ggaaggactg cccacgtgca gaggggcca agaaagtggc cttgtcctca aagcaacttg 840  
 agatgaggat cctgtgtcat ccaacagcta cagcttaggc agatgaatag cggcttccct 900  
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<210> 174  
 <211> 96  
 <212> DNA  
 <213> Homo sapien

<400> 174  
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 acaataaaag taataaaaaa taccatatta caacta 96

<210> 175  
 <211> 96  
 <212> DNA  
 <213> Homo sapien

<400> 175  
 catggaggaa cccacagatg tgaattcaaa caactgcagt tcaaaaatat ttagagaaag 60  
 acaataaaag taataaaaaa taccatatta caacta 96

<210> 176  
 <211> 780  
 <212> DNA

201

&lt;213&gt; Homo sapien

&lt;400&gt; 176

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ggaatgacag gggtttggcaa tcccatagct tctgaattcc agggagggga ggagaaagat    360
gcgggtgaaa acctgctttc agagggtttt cccttggtg cctcctcaac caaactcacc     420
cacaaattgc atgtcaagtt tcccaacctc cacctaaggg agcaggctct ttcacttcag     480
agaattcaga ggcattctcga gggcatatgc cagggcaggc acagagttag gaggtggggt     540
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gctgtctggag agctggtctc tgaaaggaga atgcatgaat ctgaactaga aacagaaggg     660
cagaaggacc aggaaaagaa atgagagcca aacagagtct gagcaatgaa aggatgtttc     720
agagagctga aaacacaagc taagctaagc atcagtggac tgggagagct ctgcaaaata     780

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&lt;210&gt; 177

&lt;211&gt; 839

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 177

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cctcacctgg cggtttgtata gctccttcta gcccccttat ctattccag ctgcatgaca      60
gccaagttag acagggaccc atccacatcc cccttagaga tcaaacaatt gtgtctcgaa     120
gcagcaaacc tccttctcag ccattcacctg ctgggcatgt tctgggtgag cctggggaag     180
atgatatgtg ccccatcgtt aaaagtgaag gaacgtgcat ctcaggggct ccacagagca     240
cccagagtcc agtgctgcag aggcaggatg ggcccaggcc cctcaagccc attcttctct     300
tggctcctgt tccatctcgg cagtgtctcc tccaggagg atgtgggatt tgatacgtgg     360
gaatgacagg gtttggcaat cccatagctt ctgaattcca gggaggggag gagaaagatg     420
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ctgctggaga gctggtctct gaaaggagaa tgcatgaatc tgaactagaa acagaagggc     720
agaaggacca ggaaaagaaa tgagagccaa acagagtctg agcaatgaaa ggatgtttca     780

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<210> 178  
 <211> 646  
 <212> DNA  
 <213> Homo sapien

<400> 178  
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 atctcggcag tgcttcctcc agggaggatg tgggatttga tacgtgggaa tgacaggggt 180  
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 gctttcagag ggttttccct tggctgctc ctcaaccaa ctcaccaca aattgcatgt 300  
 caagtttccc aacctccacc taggggagca ggctctttca cttcagagaa ttcagaggca 360  
 tctcgagggc atatgccagg gcaggcacag agtgaggagg tggggttggg ggtttttggg 420  
 cagctctggt cccctccagc cccacagagc atgcaatgtg gctgatgctg ctggagagct 480  
 ggtctctgaa aggagaatgc atgaatctga actagaaaca gaagggcaga aggaccagga 540  
 aaagaaatga gagccaaaca gagtctgagc aatgaaagga tgtttcagag agctgaaaac 600  
 acaagctaag ctaagcatca gtggactggg agagctctgc aaaata 646

<210> 179  
 <211> 521  
 <212> DNA  
 <213> Homo sapien

<400> 179  
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 gcagcaaacc tccttctcag ccatcacctg ctgggcatgt tctgggtgag cctggggaag 180  
 atgatatgtg ccccatcgta aagtgaaaga actgcatctc agggctccac agagcaccca 240  
 gagtccagtg ctgcagaggc aggatggccc agggccctca agccattct tctcttggct 300  
 cctgttccat ctcggcagtg cttcctccag ggaggatgtg ggatttgata cgtgggaatg 360  
 acagggtttg gcaatcccat agcttctgaa ttocaggag gggaggagaa agatgcgggt 420  
 gaaaacctgc tttcagaggg ttttcccttg gctgctcct caaccaaact caccacaaa 480  
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<210> 180  
 <211> 215  
 <212> DNA

203

&lt;213&gt; Homo sapien

&lt;400&gt; 180

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aaaagtgatt acatggggtt attcttggtg gagaaggtgt tgtaaccacg ggggcaaagc      60
cctaatacta tggattagct acaagatccc agtaatagct ttggattcaa aatcttcctt      120
tgcgaggctc ttctcactaa tgcagtttca tttgggctaa aattcagggg atctgagttc      180
ctgttcgact gtgcaattta ccagctacat ggacc                                215

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&lt;210&gt; 181

&lt;211&gt; 215

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 181

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aaaagtgatt acatggggtt attcttggtg gagaatgtgt tgtaaccaca tgggcaaagc      60
cctaatacta tggattagct acaagatccc agtaatagct ttggattcaa aatcttcctt      120
tgcgaggctc ttctcactaa tgcagtttca tttgggtctaa aattcagggg atctgagttc      180
ctgttcgact gtgcaattta ccagctacat ggacc                                215

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&lt;210&gt; 182

&lt;211&gt; 858

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 182

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ttagaaaaag tgtctcacat tcccgttcag gggcccaagc atctgcctcc tctcctgcac      60
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tgctgctttc tgggcagtgg cctagaactt caaggctgat gagcatatgc agaaggcagg      180
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acctggcttc tgetcagagc tgccattgtg ccttcctga catgagtga gctgggacac      360
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ggaaacagag gcagccgtgc tctgtcacta ccaatttgta caaggcacag ggcctaattg      480
ttgactttct acagcaagtc tctgtgtga gaccaggacc tcttcccagc attctaaatg      540
caagacatct caacagccca gcatgtcaga gtggcatccc gtaggatgtc tgctttctct      600
catcagtcct ggagtgcac ctcagagaat gctgtgagc agcatccgac agagactacc      660
aaciaactgg cccaggcatc tggcaccaga gaaaaatgaa ctcccagtag acagttccac      720
cacgtgacat tttcatgatt gacagccctc tcccactttc cctagcctgg cttacatgtt      780
gagaaggtag gattccccat tacgagagga ggtggtctct gagcaaccac agtgatgttt      840

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204

ccattctgga gacttacc

858

&lt;210&gt; 183

&lt;211&gt; 857

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 183

ttagaaaaag tgtctcacat tcccgttcag gggccagca tctgctcct ctccctgcaca	60
gagggctctgg gcttctcggg gcctgtaagt tggctaagcc cctcatcgga ccactggctct	120
gctgctttct gggcagtggt ctagaacttc aaggctgatg agcatatgca gaaggcagga	180
ggacacagtc tggctggctt gggcctcact agctgacaga ggggctgcc agcctgacca	240
caggggtttc atggcagga ctccagacca ctactcatc ctatctgact tcacacacca	300
cctggcttct gctcagagct gccattgtgc cttccctgac atgagtgcag ctgggacaca	360
caccagggaa aggtcttctg ctccctgcaa gtccacaggg gagaaagcgt tacctccagg	420
gaaacagagg cagccgtgct ctgtcactac caatttgtac aaggcacagg gcctaattgt	480
tgactttcta cagcaagtct cctgtgtgag accaggacct cttcccagca ttctaaatgc	540
aagacatctc aacagcccag catgtcagag tggcatcccg taggatgtct gctttctctc	600
atcagtcctg gagtcgcacc tcagagaatg cctgtgagca gcatccgaca gagactacca	660
acaaactggc ccaggcatct ggcaccagag aaaaatgaac tcccagtaga cagttccacc	720
acgtgacatt ttcatgattg acagccctct cccactttcc ctagcctggc ttacatgttg	780
agaaggtagg attccccatt acgagaggag gtggctctctg agcaaccaca gtgatgtttc	840
cattctggag acttact	857

&lt;210&gt; 184

&lt;211&gt; 392

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 184

ggggattggg gggcagtcag aaacggggca ggctcccagg ctctgctctt gtgacggagc	60
acctctgcaa gagaagacga cacgggtctc atgtgctcca aggggtgggag gtcacagagg	120
agctggcaga gaagagtccc aaaaatatcc aaggcgtgtc tcgatgagac catctgaagg	180
cggcgctttg ctccctacgc cggggacagc gcccgccaac actgtggcct ccacagcctg	240
acaaagctgt gagctgcgtg ggaagccatc ggccttggcc atggccatgc acctgcagcc	300
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attcaaatac atctatggct tttatatttat tt	392

205

<210> 185  
 <211> 392  
 <212> DNA  
 <213> Homo sapien

<400> 185  
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 acctctgcaa gagaagacga cacgggtctc atgtgctcca aggggtgggag gtcacagagg 120  
 agctggcaga gaagagtccc aaaaatatcc aaggcgtgtc tcgatgagac catctgaagg 180  
 cggcgctttg ctccctacgc cggggacagc gcccgccaac actgtggcct ccacagcctg 240  
 acaaagctgt gagctgcgtg ggaagccatc ggccttggcc atggccatgc acctgcagcc 300  
 caaatggaga cagtttctcc tctgcatctc atcacagatg ttaccctggg tctgcaactg 360  
 attcaaatac atctatggct tttattttat tt 392

<210> 186  
 <211> 632  
 <212> DNA  
 <213> Homo sapien

<400> 186  
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 aaccttaaat tcaagggtgct gatcttaatc taaaaaacct catgtgggtt gggttctggg 180  
 taccttagag atttgactct aagcaccocaa aggcatttaa gattagatga aatacttggc 240  
 cgatgggttca ctactgaaac ctgatgaact ggaatcctct gattttaatt gcctttgggt 300  
 gcttagagtc aaatctctaa ggtaaccaga acccaaacca catgagggtt ttagatttaa 360  
 gatcagcacc ttgaatttaa ggttttgtgg ctagagggtt agatttgatt ggaattacat 420  
 cgtaattttt tgttaaattg ttgaataagc aacttcccaa gccttgtgtg tagaagctag 480  
 attaaaagtc aagtttctac ttaaccagaa tctctgtttt gagtttttaa attcaactgg 540  
 tgatgtctaa atcttaagga tattgtaagt tccttaacta gtctgttcca ttttcctgag 600  
 ttttcacatc acctctctac ctcttgtgta ga 632

<210> 187  
 <211> 457  
 <212> DNA  
 <213> Homo sapien

<400> 187  
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 ggtgcttaga gtcaaactct taaggtaacc agaaccctaaa ccacatgagg ttttttagat 180

206

taagatcagc accttgaatt taaggttttg tggctagagg tttagatttg attggaatta	240
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tagattaaaa gtcaagtttc tacttaacca gaatctctgt tttgagtttt taaattcaac	360
tggatgatgc taaatcttaa ggatattgta agttccttaa ctagtctgtt ccattttcct	420
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<210> 188  
 <211> 680  
 <212> DNA  
 <213> Homo sapien

<400> 188	
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ggaggtagag cttgcagtga cccaagattg tccaatgca ctgcacgcct gggtagacaga	180
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cacctatct gaaaagagac acacaaaac agaggattcc agttcatcag gtttcagtag	300
tgaaccatcg gccaaagtatt tcatctaac ttaattgcct ttgggtgctt agagtcaa	360
ctctaaggta accagaaccc aaaccacatg aggtttttta gattaagatc agcacctga	420
atttaagggt ttgtggctag aggttttagat ttgattggaa ttacatcggt aatttttgtt	480
aaattgttga ataagcaact tccaagcct tgtgtgtaga agctagatta aaagtcaagt	540
ttctacttaa ccagaatctc tgttttgagt ttttaaattc aactgggtgat gtctaaatct	600
taaggatatt gtaagttcct taactagtct gttccatttt cctgagtttt cacatcacct	660
ctctacctct tgtgtagatt	680

<210> 189  
 <211> 605  
 <212> DNA  
 <213> Homo sapien

<400> 189	
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gagcttgtag tgagccaaga ttgtgccaat gcactgcagc ctgggtgaca gactgagact	120
gtgtctgaaa aacaaacaaa caaacaaaac ccagaatgg ttggtcaccc tatctgaaaa	180
gagacacaca aaatcagagg attccagttc atcaggtttc agtagtgaac catcgccaa	240
gtatttcac taatcttaatt tgcctttggg tgcttagagt caaatctcta aggttaaccag	300
aacccaaacc acatgagggt ttttagatta agatcagcac cttgaattta aggttttgtg	360

207

gctagagggt tagatttgat tggaattaca tcgttaattt ttgttaaatt gttgaataag 420  
 caacttccca agccttggtg gtagaagcta gattaaaagt caagtttcta ctttaaccaga 480  
 atctctgttt tgagttttta aattcaactg gtgatgtcta aatcttaagg atattgtaag 540  
 ttccttaact agtctgttcc attttcctga gttttcacat cacctctcta cctcttggtg 600  
 agatt 605

<210> 190  
 <211> 445  
 <212> DNA  
 <213> Homo sapien

<400> 190  
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 caaatctcta aggttaaccag aacccaaacc acatgagggt ttttagatta agatcagcac 180  
 cttgaattta aggttttgtg gctagagggt tagatttgat tggaattaca tcgttaattt 240  
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 caagtttcta ctttaaccaga atctctgttt tgagttttta aattcaactg gtgatgtcta 360  
 aatcttaagg atattgtaag ttccttaact agtctgttcc attttcctga gttttcacat 420  
 cacctctcta cctcttggtg agatt 445

<210> 191  
 <211> 578  
 <212> DNA  
 <213> Homo sapien

<400> 191  
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 gacactgggc agaggtttta ggcttttgca tcttgacgtg ggagatagag agcctgtgag 180  
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 ggttgacagc tcagatcaaa agctccattc ctgaaggctg ggacagcatt aggggacagg 300  
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 tccgaagaaa aagaaggctc cctctctagt gggttgaagc cccaggttca cagcagttct 420  
 cagcatgggtg ccccagcaga ctggcctggg tatcgggaga cactactgca tgatctgtca 480  
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 aactttttaa taactaagta aataaggctg gagcacac 578

<210> 192  
 <211> 744  
 <212> DNA  
 <213> Homo sapien

<400> 192  
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 ccgccagcct cggcttccca aagtgtctggg attacaggca ggagccactg tgtccagcct 180  
 tatttactta gttatttaaa agttaaaca ttttttaaaa aggtaagcag ttttccaaca 240  
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 gagtttctgc tttgtcacct tactcctgtc ccctaagtct gtcccagcct tcaggaatgg 480  
 agcttttgat ctgagtctgc aacctgattc ctgaaagcta ttgatcaagc accctgccag 540  
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 agcctaaaac ctctgccag tgtcttggtc aaagggttta ggcttttgca tcttgacgtg 660  
 ccaggcagct cttggggaag agtttctgct ttgtcacctt actcctgtcc cctaagtctg 720  
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<210> 193  
 <211> 742  
 <212> DNA  
 <213> Homo sapien

<400> 193  
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 ccgccagcct cggcttccca aagtgtctggg attacaggca ggagccactg tgtccagcct 180  
 atttacttag ttatttataaa gtaaaacatt ttttataaaag gtaagcagtt ttccaacact 240  
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 ggggaccttc tttttcttcg gagtctgaaa tgaagggtgc caggcagctc ttggggaaga 420  
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 cttttgatct gagtctgcaa cctgattcct gaaagctatt gatcaagcac cctgccagcg 540  
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 cctaaaacct ctgccagtg tcttgggtcaa aggttttagg cttttgcatc ttgacgtgcc 660

209

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ccagccttca ggaatggagc tt 742

<210> 194  
 <211> 350  
 <212> DNA  
 <213> Homo sapien

<400> 194  
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 acatcagcag ctcccttggg caaagagaaa ctgccccgac agaaagaaac atttttgggt 180  
 attagttaaa cattgcctga atatttggat cttgcttttt tctctctcc tccaagaata 240  
 agttttaatg gcctggggtt acagatccac acgggaccta aggagggagc ggttgatttg 300  
 actttcactt gatttactaa agcaattgaa tttgtcgggg gaaatttgat 350

<210> 195  
 <211> 350  
 <212> DNA  
 <213> Homo sapien

<400> 195  
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 agggaaagat tccatgtagg actatgggga ggggagaatg catttgaagc tctctctaag 120  
 acatcagcag ctcccttggg caaagagaaa ctgccccgac agaaagaaac atttttgggt 180  
 attagttaaa cattgcctga atatttggat cttgcttttt tctctctcc tccaagaaca 240  
 agtttttagtg gcctggggtt agagagccac acgggaccta aggagggagg ggttgatttg 300  
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<210> 196  
 <211> 553  
 <212> DNA  
 <213> Homo sapien

<400> 196  
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 caccaggaga tcctatgcat ctttaaataa gaatgaagaa gtcgttttgt acatacacia 120  
 atgtggaata ttatgtagct gtgttaaatt taaaaatca aatgcagaag atctctgtgt 180  
 actaatagga aaatatatct tggacttttc cagtgaagaa agcaaagtgc attggccgtg 240  
 ctagctcctg cttgactttc taatccctgg ggcccaatgc tgtacttggg tttggttttg 300  
 tttattttgt tttcttcttc tgtcctttcc aaacacgcac acttattggg tctattgttt 360



210

gcctaaccct ttgatactat acccagcagc tctcatcttt ccacctattc agacctgtgg 420  
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 agaaagaaat gca 553

<210> 197  
 <211> 554  
 <212> DNA  
 <213> Homo sapien

<400> 197  
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 aatgtggaat attatgtagc tgtgttaaata tttaaaaatc aaatgcagaa gatctctgtg 180  
 tactaatagg aaaatatatt ttggactttt ccagtgaag aagcaaagtg cattggccgt 240  
 gctagctcct gcttgacttt ctaatccctg gggcccaatg ctgtacttgg ttttggtttt 300  
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 cacaatatgg actatcctgg catgctagtg tctttcttct taagcttcat cttgggctct 540  
 tagaaagaaa tgca 554

<210> 198  
 <211> 106  
 <212> DNA  
 <213> Homo sapien

<400> 198  
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 agaaaatctt tggaacataa gactacgtga agaggctggg tgtggt 106

<210> 199  
 <211> 106  
 <212> DNA  
 <213> Homo sapien

<400> 199  
 caagactctg tctcaaaaaa agaaaaaag acccataagg cttttagaag aaaatacagg 60  
 agaaaatctt tggaacataa gactacgtga agaggctggg tgtggt 106

<210> 200  
 <211> 104  
 <212> DNA

211

&lt;213&gt; Homo sapien

&lt;400&gt; 200

caagactctg tctcaaaaaa agaaaaaaag acccataagg cttttagaag aaaatcagga 60

gaaaatcttt ggaacataag actcgtgaag aggctgggtg tgggt 104

&lt;210&gt; 201

&lt;211&gt; 719

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (76)..(155)

&lt;223&gt; n=a,c,g or t

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (620)..(620)

&lt;223&gt; n=a,c,g or t

&lt;400&gt; 201

ttgttcccaa aaaatgttta caatggacat gtattttatg tgaacttttt aaaaagttac 60

ttctattgta agaaannnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 120

nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnagaag aaaacttgat agccttgatg 180

gatataaaaa gaaaacttat ctaattataa gacatcccct attattgaat agaaagtctt 240

agaattataa atacagcaat tctgtcttca gttagtctat aagtgtaatg gttatattag 300

aacagcccaa gtttactgca gttacaaatt aaccctgaaa tccccctgtc tgacgctgag 360

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atctgaaaga agtaccacgc tcagaggctg tggcaggaaa agaaggaggg gagtcaaaat 540

ccagcaacta aatgttttgg cctggaaaca tcacatgaca cttggctatt ggccagacta 600

atcacataac ccacctgan tgcagggagg caaggaactt cagtctttcg tacgtgcagg 660

aatcagaaaa gatccagata ctggtgaata ctcgtgggtt tcaataaaaa taccattga 719

&lt;210&gt; 202

&lt;211&gt; 449

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 202

tgatggatat aaaaagaaaa cttatctaata tataagacat cccctattat tgaatagaaa 60

gtcttagaat tataaataca gcaattctgt cttcagttag tctataagtg taatggttat 120

212

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attagaacag cccaagttaa ctgcagttac aaattaaccc tgaaatcccc ctgtctgacg      180
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catagaggtc tagaccatt caggggtcta gactctctga ggctgtgcca tcttgagtt      300
acatcatctg aaagaagtac cacgctcaga ggctgtggca ggaaaagaag gaggggagtc      360
aaaatccagc aactaaatgt tttggcctgg aaacatcaca tgacacttgg ctattggcca      420
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<210> 203  
 <211> 752  
 <212> DNA  
 <213> Homo sapien

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<400> 203
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<210> 204  
 <211> 1024  
 <212> DNA  
 <213> Homo sapien

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<400> 204
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&lt;210&gt; 205

&lt;211&gt; 2981

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 205

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215

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 <212> DNA  
 <213> Homo sapien

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216

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<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo 'sapien

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<400> 209

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217

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218

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&lt;210&gt; 210

&lt;211&gt; 4624

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 210

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220

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228

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&lt;211&gt; 889

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 216

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229

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&lt;211&gt; 2106

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 217

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230

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231

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233

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234

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 <213> Homo sapien

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236

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&lt;211&gt; 2861

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 223

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237

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<400> 224

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&lt;211&gt; 1018

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 225

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240

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&lt;210&gt; 226

&lt;211&gt; 1844

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 226

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241

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&lt;210&gt; 227

&lt;211&gt; 1003

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 227

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242

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 <213> Homo sapien

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244

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<210> 233  
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245

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 233

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&lt;210&gt; 234

&lt;211&gt; 1808

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

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&lt;222&gt; (1690)..(1690)

&lt;223&gt; n=a,c,g or t

&lt;400&gt; 234

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246

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&lt;210&gt; 235

&lt;211&gt; 1271

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 235

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247

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&lt;210&gt; 236

&lt;211&gt; 2520

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 236

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248

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&lt;211&gt; 2489

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&lt;213&gt; Homo sapien

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250

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251

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&lt;211&gt; 2120

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 239

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253

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254

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&lt;211&gt; 2280

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 242

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&lt;213&gt; Homo sapien

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&lt;211&gt; 1263

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&lt;213&gt; Homo sapien

&lt;400&gt; 245

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 <213> Homo sapien

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260

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 <213> Homo sapien

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 <213> Homo sapien

261

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262

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<223> n=a,c,g or t

<220>  
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<223> n=a,c,g or t

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263

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 <212> DNA

264

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (84)..(84)

&lt;223&gt; n=a,c,g or t

&lt;400&gt; 253

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265

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aattaagcgg tc 2712

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&lt;210&gt; 254

&lt;211&gt; 2736

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 254

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266

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 <213> Homo sapien

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268

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<213> Homo sapien

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<212> DNA  
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<210> 259  
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<212> DNA  
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269

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&lt;210&gt; 260

&lt;211&gt; 1406

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 260

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270

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 <212> DNA  
 <213> Homo sapien

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<210> 262  
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 <212> DNA  
 <213> Homo sapien

271

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 <212> DNA  
 <213> Homo sapien

<400> 263  
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272

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 agagttattt gataatttta tttgcttttg agg 1413

&lt;210&gt; 264

&lt;211&gt; 1533

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 264

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&lt;210&gt; 265

&lt;211&gt; 1693

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 265

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 ttaagatata gtg 1693

&lt;210&gt; 266

&lt;211&gt; 1715

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 266

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 ttatgtacgt gactatgtct aattaagata tagtg 1715

&lt;210&gt; 267

&lt;211&gt; 1747

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 267

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tcaaggttcg tccatcatgt cgcataatc ctttattcct ttttatgggc aaataaattt 1740
cattgta 1747

```

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<210> 268
<211> 665
<212> DNA
<213> Homo sapien

```

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<400> 268
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tgaggcctcc tctccaagtc ccttcccca caagcctagc catggacctg gcttgaacaa 120
ggccatggca gatacagtca gttttgcccc ctccacatct cccatctccc tcttcttcta 180
tgagtgcctc ccttctccca ctccctatgc acctgtgggg ttccaccact ttgccctctt 240
tgtgcagaaa ggggtgccag gcctgggtcaa gcagggccct cctccttct gcctatagcg 300
attgggtcag ggatgagcac atggctggca gaactgggta aaagaagatt ttattccact 360
ggcctgaaag ctagcagggc atgagcctgg aactgctgcc agctatatta ttatctcata 420
aggagatcct atttgagggc taagccagca cagagcaagc acagttgagg gacaaagata 480
gagtgcctat ttagtgatct tagtgatcag cccgtggatc aagccatgcc tgaagcctaa 540
cccagccttt ccagaaacat gagtccataa agtttttttt gttttttgct taagcccatt 600
tcagttggac tttctgtccc ttgcaccagc ttttgccttg ctctctgcc acagacacag 660
ggccc 665

```

```

<210> 269
<211> 385

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277

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 269

```

ccctccttct gcctatagcg attgggtcag ggatgagcac atggctggca gaactgggta      60
aaagaagatt ttattccact ggcctgaaag ctagcagggc atgagcctgg aactgctgcc      120
agctatatta ttatctcata aggagatcct atttgagggc taagccagca cagagcaagc      180
acagttgagg gacaaagata gagtgcctatc ttagtgatct tagtgatcag cccgtggatc      240
aagccatgcc tgaagcctaa ccagccttt ccagaaacat gagtccataa agtttttttt      300
gttttttgct taagcccatt tcagttggac tttctgtccc ttgcaccagc ttttgccttg      360
ctcctctgcc acagacacag ggccc                                     385

```

&lt;210&gt; 270

&lt;211&gt; 733

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (502)..(520)

&lt;223&gt; n=a,c,g or t

&lt;400&gt; 270

```

tttatcacca tgtcgtggct ttaacaacca atgccctatt ttccactgga aataaagtca      60
atagtgcctt taaactaaaa aagatgagaa atccaatttg agaaaacaca gaattgattt      120
agaaaactca ttcttaagat tctcttctctc tagaaccact tctggaacaa aatatctttt      180
ggtcagcggt gaaacggagt aacaaaatca atatgacata taaaaatgat ttattgcaag      240
gaactttctt atgccactgt gggactggct aagcaactgc aaaaaacata tggctatacc      300
ccaggatggc tcagatggaa cactaaccga cgagaggaag atgctactaa aagggtgcaat      360
ttcttttttc aaagaagctt cagctctact tttaaataat ttcaagtgat tcatcaggcc      420
cactgacatt atctcacata atatccctac tcaaagccaa ctgattatgg gctaaatatc      480
tacaaaatgc cttocatata gnnnnnnnnnn nnnnnnnnnn tactgtttga ttaaataact      540
agggactgta gtctaggcat gttgtaatta aaattgatac cacacagatc ctcatcatca      600
gaaaactggt taaggaaaaa ttaatatcca gtacaccagg atacagcagg cattagaaat      660
gaggttggag gtcaacttat ttatacagcc tttaacatta gtgtcatatt aggacaatcc      720
tgtaggagc aag                                              733

```

&lt;210&gt; 271

&lt;211&gt; 475

&lt;212&gt; DNA

278

&lt;213&gt; Homo sapien

&lt;400&gt; 271

```

tttatcacca tgtcgtggct ttaacaacca atgccctatt ttccactgga aataaagtca      60
atagtgcctt taaactaaaa aagatgagaa atccaatttg agaaaacaca gaattgattt    120
agaaaactca ttcttaagat tctcttctct tagaaccact tctggaacaa aatatctttt    180
ggtcagcggt gaaacggagt aacaaaatca atatgacata taaaaatgat ttattgcaag    240
gaactttctt atgccactgt gggactggct aagcaactgc aaaaaacata tggctatacc    300
ccaggatggc tcagatggaa cactaaccca cgagaggaag atgctactaa aagggtgcaat    360
ttcttttttc aaagaagctt cagctctact tttaaataat ttcaagtgat tcatcaggcc    420
cactgacatt atctcacata atatccctac tcaaagccaa ctgattatgg gctaa      475

```

&lt;210&gt; 272

&lt;211&gt; 403

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 272

```

ctttgtttct tgtgaccatg tatttttgca tattaagttc cgaatgtatg aatgcattta      60
ttcaactagt ctactccact ttcacatctt aaaataactc ttgttgtttt atttcactat    120
aaaagttgca aatgttcatt gaatataatg tgcaaatgtg gaaaaatata aaggaaattc    180
atcaaaatgt atcttaattt tataagtgat cttttccttc tgtttttcca ggcttttagt    240
caaattttta aatgagtttt cctcttatca tgaaacattc tttaaaacta ttttggtagt    300
taattatfff gttgtacagt ttatatactg ttgaaaataa attttcctct gggatcttag    360
tttcttcag tttttcacca tgataaaaat aatattagta gag      403

```

&lt;210&gt; 273

&lt;211&gt; 403

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 273

```

ctttgtttct tgtgaccatg tatttttgca tattaagttc cgaatgtatg aatgcattta      60
ttcaactagt ctactccact ttcacatctt aaaataactc ttgttgtttt atttcactat    120
aaaagttgca aatgttcatt gaatataatg tgcaaatgtg gaaaaatata aaggaaattc    180
atcaaaatgt atcttaattt tataagtgat cttttccttc tgtttttcca ggcttttagt    240
caaattttta aatgagtttt cctcttatca tgaaacattc tttaaaacta ttttggtagt    300
taattatfff gttgtacagt ttatatactg ttgaaaataa attttcctct gggatcttag    360
tttcttcag tttttcacca tgataaaaat aatattagta gag      403

```

279

<210> 274  
 <211> 478  
 <212> DNA  
 <213> Homo sapien

<400> 274  
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 gtctctgtga aatcatgttg atgtaattga ttaacaaaaa taatttagaa aatacgtcag 120  
 gcacagttga tggcttctca atatctgctt tgcattttta aacaaatcaa gaatgtaatt 180  
 ttaacttttg cttatgggtca ttcttatgac tacacggaaa gggatggaat catacttact 240  
 tgtcttatac atggactgtt tttagttaac aataacataa ctacacaaag gaaaggaaat 300  
 gtttacattt taaaaaatta ctgtaatta catctggtat ttttcagatt atgcataaaa 360  
 taatatgagt ttgactattg tatcagaata ttttaaatcaa atcctgcaat ttatattaac 420  
 ttaaaaaaac atctggtaaa gactgggtgt ggcagctcac gcctgtaatc ccagcact 478

<210> 275  
 <211> 1109  
 <212> DNA  
 <213> Homo sapien

<400> 275  
 taatacgacc acatagggat ttggccctca gcgagaattc ggcagagtgg gggttttgcca 60  
 cgttggccag gctggtctca aactcctgaa ctcaagtaat ttgcctgctt cggcctccca 120  
 gagtcctggg attacagtgc tgagccatcg cgcctggccg tgatagaaac tttcagctga 180  
 ggagtctata tgccatacta ctctatgtgg catcttttagg tctctgtgaa atcatgttga 240  
 tgtaattgat taacaaaaat aatttagaaa atacgtcagg cacagttgat ggcttctcaa 300  
 tatctgcttt gcatttttaa acaaatacag aatgtaattt taacttttgc ttatgggtcat 360  
 tcttatgact acacggaaag ggatggaatc atacttactt gtcttataca tggactgttt 420  
 ttagttaaca ataacataac tacacaaagg aaaggaaatg tttacatttt aaaaaattac 480  
 tgtcaattac atctggtatt tttcagatta tgcataaaat aatatgagtt tgactattgt 540  
 atcagaatat tttaatcaaa tcctgcaatt tatattaact taaaaaaca tctggtaaag 600  
 actgggtgtg gcagctcacg cctgtaatcc cagcactttg ggaggccgag gctggatgga 660  
 tgattgcttg agcgcaggag ttctagacca gcctgggcaa tacagggaga ccctgtctct 720  
 atttcaaaaa taaataaata ggccccggtg tgtgatgttc cccttcctgt gtccatgtgt 780  
 tctcaaaaaa aaaaaaaaaa taaaaataaa aataaataaa taaataaccg gtaaagatgt 840  
 actgtttcta ctgcagtta taatatttca tttattaaga aagatatcat ctacagctttc 900  
 aaattcaaca tagccctcaa tttatgacat aagttttata cttagtattt tataatttct 960

280

taatttttgtt ataaacttga aaatgtagaa tatgggggtcc aaaatctgtt gaacatttgt 1020  
 tcagctagtt aggtttcaac attaatcata tacattaata gtatcttcat gtacgctatg 1080  
 tgaaggggtgt tttttataag aaataggaa 1109

<210> 276  
 <211> 1174  
 <212> DNA  
 <213> Homo sapien

<400> 276  
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 cttcggcctc ccagagtcct gggattacag tcgtgagcca tcgcgcttg ccgtgataga 120  
 aactttcagc tgaggagtct atatgccata ctactctatg tggcatcttt aggtctctgt 180  
 gaaatcatgt tgatgtaatt gattaacaaa aataatttag aaaatacgtc aggcacagtt 240  
 gatggcttct caatatctgc tttgcatttt taaacaaatc aagaatgtaa ttttaacttt 300  
 tgcttatggc cattcttatg actacacgga aagggatgga atcactactta cttgtcttat 360  
 acatggactg ttttttagtta acaataacat aactacacaa aggaaaggaa atgtttacat 420  
 tttaaaaaat tactgtcaat tacatctggc atttttcaga ttatgcataa aataatatga 480  
 gtttgactat tgtatcagaa tattttaatc aaatcctgca atttatatta acttaaaaaa 540  
 acatctggta aagactgggt gtggcagctc acacctgtaa tcccagcact ttgggaggcc 600  
 gaggcctggat ggatgattgc ttgagcgcag gagttctaga ccagcctggg caatacaggg 660  
 agaccctgtc tctatttcaa aaataaataa ataggccccg gtgtgtgatg tcccccttc 720  
 tgtgtccatg tgttctcaa aaaaattaaa aaataaaaaat aaaaataaat aaataaataa 780  
 ccagtaaaga tgtactgttt ctactgcagt ttataatatt tcatttatta agaaagatat 840  
 catctcagct ttcaaattca acatagccct caatttatga cataagtttt atacttagta 900  
 ttttataatt tcttaatttt gttataaact tgaaaatgta gaatatgggg tccaaaatct 960  
 gttgaacatt tgttcagcta gttaggtttc aacattaatc atatacatta atagtatctt 1020  
 tatgtaagga tatgtgaagg gtgtttttct ttataagaaa attagttaa tcagggtgagc 1080  
 tgatacttag gattatacat atatctatga taaaattgaa agtaattgtg gttgttcttt 1140  
 agagaacgtg ttttgatttt gacttagtat tggg 1174

<210> 277  
 <211> 525  
 <212> DNA  
 <213> Homo sapien

<400> 277

281

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tttcattggt actagaatgt catctttcgc cgacaagttg ttccccagca gaatcctgct      60
gctcctggca caaaacaagc agatgaagag gtaaataacc ttgtgcaa atcttctcgg      120
cgctgagcct gccgcgcct aagcgcgctg ttattctagc ttatccgcaa ggactctgct      180
aaattaggca ggatgacatg tggttgttct ccgttaaagc agatgggtac aatgaggctc      240
agagagatga gatgatttgg caggtaaatg agagcactag gctggcactc ggatcggcct      300
gctcccagtg gagggctttc tgccaccat gagccagcca tgtaaaatga gcaggggtgg      360
gttgatgag tgaatccctt aaggagcttg taaggatgca gatcaccgg ccctggagat      420
cctgagtctg gaaacagtg gattggtgga ttctaagga ccttttagagg ctcaagatta      480
tccactgtgc ccagcctcag atctcacagg gccgggtatc tctttt                    525

```

&lt;210&gt; 278

&lt;211&gt; 402

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 278

```

gcggccgctg ggagcggggt tcgatcccgat gatgccgtcg tgggtgccgg ccagagaaga      60
gctccggagg ccggggcggc cggcgggctg gcgaatgtca tctttcccaa caagttgttc      120
ccagcagaat cctctctcct ggcacaaaac aagcagatga agagcagccc tgagaggtag      180
acacagcgga gatttttttc acccgcatctg tacagaagag aaaatgaagc ttgccccaac      240
ctgcaggaga tcccctcacc ttgcaaaaga gccaaactgt ggctaaactg ggatcttcag      300
tccctggacc atttagcttg actaagagaa caggaaatgga ggccaaaaga tctacaaaat      360
gctcacacag agaagatgac agcttctaca aataaatgtc aa                        402

```

&lt;210&gt; 279

&lt;211&gt; 583

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 279

```

gcggccgctg ggagcggggt tcgatcccgat gatgccgtcg tgggtgccgg ccagagaaga      60
gctccggagg ccggggcggc cggcgggctg gcgaatgtca tctttcccaa caagttgttc      120
ccagcagaat cctctctcct ggcacaaaac aagcagatga agaggtaaat gaccttgtgc      180
aaatctcttc tcccgtgag cctgcccccc aaccctgtt attctagcta tcccaaggac      240
tctgcaaatt aggcaggatg acagtgggtg ttcccgttaa acagatggga acaatgaggc      300
tcagagagat gagatgattt ggcagggtta tgagagccta ggctggcact cggatcggcc      360
tgctcccagt ggagggcttt ctgccacca tgagccagcc tgtaaaatga gcaggggtgg      420
gttgatgag tgaatccctt aaggagcttg taaggatgca gatcaccgg ccctggagat      480

```



282

cctgagtctg ggaaacagtg gattggtgga ttcctaagga ccttttagagg ctcaagatta 540  
 tccactgtgc ccagcctcag atctccaggc cgggtatctc ttt 583

<210> 280  
 <211> 781  
 <212> DNA  
 <213> Homo sapien

<400> 280  
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 ccaggcacct ggcgaggaag ccatggtctc ttccttcctt gacttagaac aactaggagg 120  
 ctctaggtt cagtcttact gggaagggga tgggaatgtg ggccaaagga cagggcagag 180  
 gctgatctaa atacgtgggc cagctccact gaggaaactg agatggacca gtgtggcgtg 240  
 gaagaaacca aggggagcag ccaaagtgtc tcttctccag gctgcctggc acagagctgg 300  
 gcacacaacc aaccctgcag accagctgtc caatgggcaa gggaaggagc aaggcaggtc 360  
 catctgcagt ctcggtgctt gggaaggtga gacagtgcag ggcataggag gctgactcca 420  
 cagtggacag agaagacttt caggagatc agctcagctc agtctgaggg gcagggacag 480  
 gaggagatag cgtttctgcg gttatcagga agggaagtgg aggaggcagc caggaagata 540  
 tcgggaagaa agaggaaggg cgtgtgctag atcccgaaga ggaaaaagca gctgaattta 600  
 gcagcctcag ggggtgtgaag gtcaaaagta tcaaggaatc ttaagcccag ggttctgggc 660  
 caagaaagca gcactctctc tcatttacat gggcatctga gatgaaacct ggtgtccggg 720  
 gacttctacc aacctaggat tcgtggggga gggcagtggt actggttcag aacgtggctc 780  
 a 781

<210> 281  
 <211> 1253  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (755)..(870)  
 <223> n=a,c,g or t

<400> 281  
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 ccaggcacct ggcgaggaag ccatggtctc ttccttcctt gacttagaac aactaggagg 120  
 ctctaggtt cagtcttact gggaagggga tgggaatgtg ggccaaagga cagggcagag 180  
 gctgatctaa atacgtgggc cagctccact gaggaaactg agatggacca gtgtggcgtg 240

283

```

gaagaaacca aggggagcag ccaaagtcc tcttctccag gctgcctggc acagagctgg 300
gcacacaacc aaccctgcag accagctgtc caatgggcaa gggaaggagc aaggcaggtc 360
catctgcagt ctcggtgct ggggaaggta gacagtgcag ggcattggag gctgactcca 420
cagtggacag agaagacttt caggagatc agctcagctc agtctgaggg gcagggacag 480
gaggagatag cgtttctgcg gttatcagga aggggaagtgg aggaggcagc caggaagata 540
tcgggaagaa agaggaaggg cgtgtgctag atcccgaaga ggaaaaagca gctgaattta 600
gcagcctcag ggggtgtgaag gtcaaaagta tcaaggaatc ttaagcccag gggtctgggc 660
caagaaagca gcactctctc tcatttacat gggcatctga gatgaaacct ggtgtccggg 720
gacttctacc aacctaggat tcgtggggga gggcnnnnnn nnnnnnnnnn nnnnnnnnnn 780
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 840
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn tatagggttg ctctaaagat tagacaaggc 900
caagtgttca gaacaatact ggcatataca aagagctcca aaattttatt tttcagttac 960
tttgctccaa tcgggtaact ccagggagag tgtcacagag caggacagca aggacagcac 1020
ctacagcctc agcagcacc cagcgtgag caaagcagac tacgagaaac acaaagtcta 1080
cgctgcgaa gtcacccatc agggcctgag ctgcccgtc acaaagagct tcaacagggg 1140
agagtgttag agggagaagt gccccacct gtcctcagt tccagcctga cccctccca 1200
tcctttggcc tctgaccctt tttccaaggg gacctacccc tattgcggtc ctc 1253

```

&lt;210&gt; 282

&lt;211&gt; 781

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 282

```

ggggttaggg gcctgaagat ctggtgtctg atgtttgcag agcccaaccc tggaagaatg 60
ccaggcacct ggcgaggaag ccatggtctc ttccttcctt gacttagaac aactaggagg 120
ctcctaggtt cagtcttact ggggaagggga tggaatgtg ggccaaagga cagggcagag 180
gctgatctaa atacgtgggc cagctccact gaggaaactg agatggacca gtgtggcgtg 240
gaagaaacca aggggagcag ccaaagtcc tcttctccag gctgcctggc acagagctgg 300
gcacacaacc aaccctgcag accagctgtc caatgggcaa gggaaggagc aaggcaggtc 360
catctgcagt ctcggtgct ggggaaggta gacagtgcag ggcattggag gctgactcca 420
cagtggacag agaagacttt caggagatc agctcagctc agtctgaggg gcagggacag 480
gaggagatag cgtttctgcg gttatcagga aggggaagtgg aggaggcagc caggaagata 540
tcgggaagaa agaggaaggg cgtgtgctag atcccgaaga ggaaaaagca gctgaattta 600

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284

gcagcctcag ggggtgtgaag gtcaaaagta tcaaggaatc ttaagcccag ggttctgggc 660  
 caagaaagca gcactctctc tcatttacat gggcatctga gatgaaacct ggtgtccggg 720  
 gacttctacc aacctaggat tcgtggggga gggcagtggg actgggttcag aacctggctc 780  
 c 781

<210> 283  
 <211> 969  
 <212> DNA  
 <213> Homo sapien

<400> 283  
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 ccatttcctt tttagcctgg agagaagccc ctgtcaccac gtttattttc atttctctct 180  
 gcggagaaga tccatctaac ccctttcttg cccagagtc cagggaaagg atgatcactg 240  
 tcagaagtcg tggcgcgga gccactggg cgctttgtca cattccaccg aaagtccga 300  
 cttggtgaca gtgtgcttcc ctccctcgc caacagttcc gagtgagctg tgcttttagct 360  
 ctctgtggggg tgggtcaagg gaggatttga agagtcattg cccacttta cccttttgga 420  
 gaaatggctt gaaatttgct gtgacacggg cagcatggga atagtccttc ctgaaccctg 480  
 gaaaggagct cctgccagcc ttgcacacac tttgtcctgg tgaaaggcag ccctggagca 540  
 ggtgtttttt tggaactcca aacctgcca cccaacttgc ttctgaaagg gactctaaag 600  
 ggtccctttc cgctcctctc tgacgccttc cctcagccag aattcccttg gagaggaggc 660  
 aagaggaaag ccatggacag gggtcgctgc taacaccgca agttcctcag accctggcac 720  
 aaaggccttg gctacaggcc tccaagtagg gaggaggggg aggagtggct gcctggccac 780  
 agtgtgacct tcagaggccc ccagagaagg acacctggcc cctgcctgcc tagaaccgcc 840  
 cctcctgtgc ccctggcct tggaaggggt atgaaatttc cgtcccctt cctccttggg 900  
 gcccaggagg agtggagggt cccgggagaa tattgtcagg ggaaggcag ggggtgtcat 960  
 gggaatgcg 969

<210> 284  
 <211> 313  
 <212> DNA  
 <213> Homo sapien

<400> 284  
 aattcacaga aagagctaga gtgtcgaggt agaggtagca attttaaatg gagatgttag 60  
 ggaaatcctc actgagaagg taacatttgg tgaaaaaaaa aaaaagtggc aagcaaggga 120  
 accatccaga tagggggcctt gtaggtggtg ggagatacgt gggatgaatt gggacacttt 180

285

gagttgcatg tttgagaagt aatatgaagg cagagagcgg ataggagctg cggaacagat 240  
 ggaccaaagt gacgggcaag atgccgcaa cacaggcagg ggcgggggca gactgagggg 300  
 gaagtgagta gca 313

<210> 285  
 <211> 1243  
 <212> DNA  
 <213> Homo sapien

<400> 285  
 aggtgtagct tgactcataa catcactaac cctactacca atggtgatgt gtaagcactt 60  
 tgtgctgggt taaagtttca aacattttct tatagagatt agatgatcta agcagtagag 120  
 tcccttaaat caaggttcag ggccaggcgc ggtggctcac gcctgtaatc ccagcacttt 180  
 aggaggccga ggtgggcgga tcacgaggtc aggagatcga gacaaccccg tctctactaa 240  
 aaaaaatgca aaacgttagc tgggcatggg ggtgggcgcc tgtagtccca gctactaggg 300  
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294

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&lt;210&gt; 296

&lt;211&gt; 870

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 296

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301

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&lt;210&gt; 297

&lt;211&gt; 1141

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 297

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302

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 <213> Homo sapien

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<220>

303

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304

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&lt;210&gt; 301

&lt;211&gt; 786

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 301

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305

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 ggcaaa 786

&lt;210&gt; 302

&lt;211&gt; 1128

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 302

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306

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<400> 305

307

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gctaacaaca ttatacctag gg                                     382

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&lt;210&gt; 306

&lt;211&gt; 452

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 306

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aaaattaagg atattctgat acatacaatt gaacaaagag attccaattt gtcatacggg      180
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&lt;210&gt; 307

&lt;211&gt; 708

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 307

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308

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319

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325

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&lt;210&gt; 319

326

&lt;211&gt; 2799

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 319

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327

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&lt;210&gt; 320

&lt;211&gt; 1064

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 320

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328

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&lt;210&gt; 321

&lt;211&gt; 2383

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 321

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329

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&lt;210&gt; 322

&lt;211&gt; 1675

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 322

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330

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&lt;210&gt; 323

&lt;211&gt; 4713

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 323

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331

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333

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&lt;210&gt; 324

&lt;211&gt; 3006

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 324

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334

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335

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&lt;210&gt; 325

&lt;211&gt; 4457

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 325

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337

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&lt;210&gt; 326

&lt;211&gt; 2712

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 326

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338

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339

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&lt;210&gt; 327

&lt;211&gt; 2785

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 327

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341

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342

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343

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&lt;210&gt; 333

&lt;211&gt; 1565

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 333

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&lt;210&gt; 334

&lt;211&gt; 1749

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 334

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346

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&lt;210&gt; 335

&lt;211&gt; 1815

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 335

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&lt;210&gt; 336

&lt;211&gt; 2132

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 336

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&lt;210&gt; 337

&lt;211&gt; 1132

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 337

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349

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&lt;210&gt; 338

&lt;211&gt; 1454

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 338

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gtctccctca accsmacwcc tcctggggcc gagcaggagt cacatccaag ggctgggtca     180
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350

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<211> 596  
<212> DNA  
<213> Homo sapien

<400> 339  
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<210> 340  
<211> 1467  
<212> DNA  
<213> Homo sapien

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351

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<210> 341
<211> 467
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (166)..(166)
<223> n=a,c,g or t

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<400> 341
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ttgagaaggg caagagcgag gtagaagagt ggtctagga gaacagttag gggctattgc 120

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352

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aattatccag caagagatct tggaccagga tggcagcagt ggaggnggta aaatgtgggt 180
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actagctgat ggctgtaaac tgggggggtca ctagctatca gatggcattt acttaaagcc 300
atggaagtag gtgagctccc ttatggagag ggaataggaa ggaggtagac cattctatca 360
aaatgctctt tctacagggc acttctcact gagatattat ttatctggga tttatattat 420
ttattcaatt tgttttgtgt ttggttctat tagaaaagct ccatagg 467

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<210> 342
<211> 783
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (166)..(166)
<223> n=a,c,g or t

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<220>
<221> misc_feature
<222> (506)..(607)
<223> n=a,c,g or t

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<400> 342
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aattatccag caagagatct tggaccagga tggcagcagt ggaggnggta aaatgtgggt 180
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ttattcaatt tgttttgtgt ttggttctat tagaaaagct ccatagggcc cgggcacggt 480
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nnnnnnntca gctccttctt tcattccaga cctgccccct ggagatcgct ccctgaatgc 660
ccctcagaca ccacaggctc ggcgagaaat tgatctcccc agcttttccc cagctctggc 720
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ctt 783

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353

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 <211> 1305  
 <212> DNA  
 <213> Homo sapien

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<210> 344  
 <211> 253  
 <212> DNA  
 <213> Homo sapien

<400> 344  
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354

tgaacaccca actcggaatc tggcccagca gacactcaga tatgagtccc caagtatttg	180
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cctgcctcta gga	253

<210> 345  
 <211> 513  
 <212> DNA  
 <213> Homo sapien

<400> 345	
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tgaacaccca actcggaatc tggcccagca gacactcaga tatgagtccc caagtatttg	180
aatgtctact gtgagcctgg aactgtcctg gggactgtgg actcaacaga aaaccacacc	240
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tggcgtcagt tcccagaaga gaaataaagc aggtacagaa tgatggtggg ggtgacggct	360
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<210> 346  
 <211> 353  
 <212> DNA  
 <213> Homo sapien

<400> 346	
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gttttaggac cttaatacat aatgacaaat agttttataa atagctgtta atgtagtgtc	180
atccataatc tgtgaatatc agcacatgat atcatgtaag ttgctctttt tttggctaata	240
taaccgacaa aaagatgcac tgttgctgtt ttaatttgcg tatctttaat tacaattaag	300
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<210> 347  
 <211> 2111  
 <212> DNA  
 <213> Homo sapien

<400> 347	
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355

tgagtagata ctaagcgggt ttgtgtcttt gttataagtt gtacttatat tttcgagaga	180
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ttaaacttgag ttccaacatg cttttagat ggtcagtcac ctacagagga caatttttct	300
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tttgagatgt ttattctcag ttgtgattta ttactgaatc tgtgtcttca tagcgactcc	420
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356

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 <211> 723  
 <212> DNA  
 <213> Homo sapien

<400> 348  
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 ccagcagcgt gtttcaaagc tggggctcca cgcatgaaga atcagcctca gtggaaagag 660  
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 tat 723

<210> 349  
 <211> 353  
 <212> DNA  
 <213> Homo sapien

<400> 349  
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358

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360

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&lt;213&gt; Homo sapien

&lt;400&gt; 355

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366

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&lt;213&gt; Homo sapien

&lt;400&gt; 357

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&lt;213&gt; Homo sapien

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410

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&lt;213&gt; Homo sapien

&lt;400&gt; 371

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&lt;210&gt; 372

&lt;211&gt; 3950

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 372

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&lt;211&gt; 4274

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&lt;400&gt; 373

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418

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&lt;210&gt; 375

&lt;211&gt; 2720

&lt;212&gt; DNA

420

&lt;213&gt; Homo sapien

&lt;400&gt; 375

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421

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&lt;211&gt; 1145

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 376

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422

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&lt;210&gt; 377

&lt;211&gt; 996

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 377

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423

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424

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 <212> DNA  
 <213> Homo sapien

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428

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 gtttaataag ccaggtatta acctgctaaa tatatta 5677

<210> 385

<211> 1026

<212> DNA

<213> Homo sapien

<400> 385

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 tataatgctt tttttttggc ttcgaaagtt ccagctgcat cttttttgat gaagtaaaaa 180  
 gcatagtgtg cgtgccctat ctccctttct tgtccacaga ttgcttaagg taggaggcat 240  
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 gaaaaa 1026

430

<210> 386  
 <211> 778  
 <212> DNA  
 <213> Homo sapien

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 aatcgatcct gcaatattct ttgcagttag ggtctgacca tttttgtttt tattgctgtg 180  
 tgctaaatac atggctatga agataaagga aaaccatgaa ataccagttc tccctttttg 240  
 cctccaacag atttccagca caagataacc gtgcaggcct ctcccaactt ggacaaacgg 300  
 cggagcctga acagcagcag ttccagtcct ccgagcagcc ccacaatgat gccccgactc 360  
 cgagccatac agtgtgagct ttctgcactg ccacgggggc tcctgtgttg acttctctcc 420  
 tttcacttga cttggattca aattgagcag atgtgttttc atagcagggt gtagatgagt 480  
 gtaggacatt tcgtagggtgc cacaactatt tgagaaacaa aacttgagca taggttcctt 540  
 agtctaattt tcttctactc acaaaaaatg aattttagat gctatgcagt tggatgagc 600  
 acctggcccc ggagtagaaa gtgaaacacc acatctcgag acattctgtt aaacacttgc 660  
 acgcaacgtt agcataacct aattctatca tcagccattt gtgtcagggt actttgaaaa 720  
 atgaaatcag gaattcagga ttaactctgt ttctttcttt gtttcgtgag gggaaaaa 778

<210> 387  
 <211> 539  
 <212> DNA  
 <213> Homo sapien

<400> 387  
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 actggtgatc ttacctcacc tacccaactt tctccaaact cacctcaagc aacagttctt 180  
 caagcctatc atgctgcatt gactttctat ttgttgaaga agctaagctg ttttaatgca 240  
 tcagggattt ttttccctct acctagaata ttctctttct agttcttcca gtggttggct 300  
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 tctataacac agtactttct aaagtaatcc agttggcttt tgggatcaga gctcttacat 480  
 gacctatttt ctgctctgtc cctaggagaa cactgacaac tattgccaat aagacacca 539

<210> 388  
 <211> 539  
 <212> DNA

431

&lt;213&gt; Homo sapien

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 tttctaaagt ttgtctcca cccttatccc actgtaacct gttaacctct ttctgtctta 420  
 tctataacac agtactttct aaagtaatcc agttggcttt tgggatcaga gctcttacat 480  
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&lt;210&gt; 389

&lt;211&gt; 276

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<400> 389  
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 accacaaatg cgaccattgt cccagtgca gaggcctaca cctgagcttt cttttctggt 180  
 gggtggcctt tgaagccagt tggctttgga agttcccttt ggagtcaact tcctgatgtc 240  
 tgggaaccctt cttaggatca tttgttcctt tttcaa 276

&lt;210&gt; 390

&lt;211&gt; 276

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<400> 390  
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 gggtggcctt tgaagccagt tggctttgga agttcccttt ggagtcaact tcctgatgtc 240  
 tgggaaccctt cttaggatca tttgttcctt tttcaa 276

&lt;210&gt; 391

&lt;211&gt; 303

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

432

<400> 391  
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 tcaacaagtt ggtggatgct gatgaaaggg gaagtagtaa atagcaaagg tctcaatgcc 120  
 tgactctgag atggagtaag gatgagctat caggactggc acttcacttc taaatgttga 180  
 gcactcaggt tttgctaaat ttataaaaagc acatgaacta actaacatcg catatttcct 240  
 taacgagaaa accagtttat ctctgtttta aacagttctg atctactcaa atacacattt 300  
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<210> 392  
 <211> 994  
 <212> DNA  
 <213> Homo sapien

<400> 392  
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 gaatcttacc caggactatg gagctccatt aattgctgtc aacacgctgg aacctatttc 180  
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<210> 393  
 <211> 802  
 <212> DNA  
 <213> Homo sapien

<400> 393

433

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ttgaatctta cccaggacta tggagctcca ttaattgctg tcaacacgct ggaacctatt      180
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aatgccagag gaagcttaag ttaaagaaag caacgatcac gcacatatat tatgttagca      300
attaggctta atcctagaat cgtgaagcca aagagaatat attaaagaga gaacagtgcc      360
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cacttctaaa tgttgagcac tcaggttttg ctaaatttat aaaagcacat gaactaacta      720
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<210> 394
<211> 790
<212> DNA
<213> Homo sapien

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<223> n=a,c,g or t

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catatctggc tacagagaaa ttctccagga gtctgcagta cactttcaca ttgtccagca      180
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aggctctaata gaaagggtag ttctcatgct ttggaagctc aagtcttct cctcaaagag      540
agtcaatgac agttatttta cagaggatth tgtagaaatg aaaggtaatt aatgccatat      600

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434

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aaaagccaaa acattacatc tgtaattgct acatagcatg tgcattgaaa gttgctggtg 660
cccataaggg acagcacttg aaggccaag gaaagagcat acccttcac ctctcagttt 720
gatttgagta ttaaatgagc tagcacacag cttggcacat gttaggcttt cagtatttac 780
cttctttctt 790

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<210> 395
<211> 790
<212> DNA
<213> Homo sapien

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<400> 395
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catatctggc tacagagaaa ttctccagga gtctgcagta cactttcaca ttgtccagca 180
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taaggcatag atctataatg aaaaacaaat cttcatttac ttctgttgcc ccatttaatg 300
attatgaaga gtaaactctt ataaagtaaa gtaatactct acttgaaagg aatattcctg 360
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agtcaatgac agttatttta cagaggattt tgtagaaatg aaaggtaatt aatgccatat 600
aaaagccaaa acattacatc tgtaattgct acatagcatg tgcattgaaa gttgctggtg 660
cccataaggg acagcacttg aaggccaag gaaagagcat acccttcac ctctcagttt 720
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cttctttctt 790

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<210> 396
<211> 690
<212> DNA
<213> Homo sapien

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<400> 396
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ttgctgatgt ttaaggaaag cagctgttgt ggaaagactt agtgggtttt tatcagagag 180
taaattttga aacaatttgt gggtttttga agtaagggtta cagtatatag tgattagaca 240
gcattttcac tctctcatga aaactgtgta gtcaaaacaa aagtaggaaa aacacatgca 300
taacccttta aatcttattt atgaaaagat aactagcgaa gatgggaaaa tcagacttgt 360

```

435

gtttaagtat catttttttta taaactagct aagtgcattt tgaaacaaaa ttcattgaggt 420  
 ctttgtggaa tgccttttcc atttttttgt tttgttttgt tttgtttttg cactcacatt 480  
 atgtctcagc aatttaatgg agggctgatt tcctaattgct ttgatccttg gtgagtgtgg 540  
 ttcaccccaa ctagggagga attcagtctt ttgttcttga ttccatgctc attgatctcc 600  
 tccactgcca ttctcagaaa caatggcagt attttgtttc catagtaatg aaactgtttg 660  
 ctctaataagg attctatagt ggtagtgcg 690

<210> 397  
 <211> 690  
 <212> DNA  
 <213> Homo sapien

<400> 397  
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 ttgctgatgt ttaaggaaag cagctgttgt ggaaagactt agtgggtttt tatcagagag 180  
 taaattttga aacaatttgt gggtttttga agtaaggtta cagtatatag tgattagaca 240  
 gcattttcac tctctcatga aaactgtgta gtcaaaacaa aagtaggaaa aacacatgca 300  
 taaccctta aatcttattt atgaaaagat aactagcgaa gatgggaaaa tcagacttgt 360  
 gtttaagtat catttttttta taaactagct aagtgcattt tgaaacaaaa ttcattgaggt 420  
 ctttgtggaa tgccttttcc atttttttgt tttgttttgt tttgtttttg cactcacatt 480  
 atgtctcagc aatttaatgg agggctgatt tcctaattgct ttgatccttg gtgagtgtgg 540  
 ttcaccccaa ctagggagga attcagtctt ttgttcttga ttccatgctc attgatctcc 600  
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 ctctaataagg attctatagt ggtaattttt 690

<210> 398  
 <211> 879  
 <212> DNA  
 <213> Homo sapien

<400> 398  
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 acgcgcatct ggtggagctc agtggaaattc aactctgctt gctctgcca gagctccacg 180  
 tcaatccgct ggtcacttgg aaggaggaag gccctgggag aggggtgcaa agccatacaa 240  
 agaaactggt caggcagaac agagaggcag gggctctgag accctgatgg gcagggtggag 300

436

gcttcttcca tgactccgc acttcatgca cccatttggc aaactgtccc atgtgtgcct 360  
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 tctggggccac ggcgactcaa gaagtgaaga gtggggctcc cactgtggat gccaggagtc 480  
 aaggtgttgc ttgaatatgg gggccacttt gagctggcca tgaacccttc tgtgacaaag 540  
 ctcttgggaa agggccattt gggacaccta ggaaggctgg cagcaccaac cagcagcccc 600  
 agggagtggg gtgtccaggc caacttgggc acagggtgga gaacagatgc cccagcaggg 660  
 ctggcactct tgaaacagaa gcaaggctgt gcacagagtt aatgcccctg acatgcctag 720  
 gactgcggta aagtagataa tgcaccttaa gtagccgaca aaactagtga caaaggggtcc 780  
 tgaggtcaca atctgaaagg agaaccatt tcactctcgg agatggcaca gaactgggttc 840  
 cagctgcaaa ccgggtggag gatacgatag ggagcatcc 879

&lt;210&gt; 399

&lt;211&gt; 879

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 399

gcctctggga gggaggagcc gagaagcaga ggacagaagc tcccgggagg ggggttaggag 60  
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 acgcgcactct ggtggagctc agtggaaattc aactctgctt gctctgccc gagctccacg 180  
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 agaaactggg caggcagaac agagaggcag gggctctgag accctgatgg gcagggtggag 300  
 gcttcttcca tgactccgc acttcatgca cccatttggc aaactgtccc atgtgtgcct 360  
 gagcaaatgt ggctgttggt gattctcggt tcataatggc cccaaaaccc aggaacagac 420  
 tctggggccac ggcgactcaa gaagtgaaga gtggggctcc cactgtggat gccaggagtc 480  
 aaggtgttgc ttgaatatgg gggccacttt gagctggcca tgaacccttc tgtgacaaag 540  
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 agggagtggg gtgtccaggc caacttgggc acagggtgga gaacagatgc cccagcaggg 660  
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 gactgcggta aagtagataa tgcaccttaa gtagccgaca aaactagtga caaaggggtcc 780  
 tgaggtcaca atctgaaagg agaaccatt tcactctcgg agatggcaca gaactgggttc 840  
 cagctgcaaa ccgggtggag gatacgatag ggagcatcc 879

&lt;210&gt; 400

&lt;211&gt; 577

&lt;212&gt; DNA

437

&lt;213&gt; Homo sapien

&lt;400&gt; 400

```

agcttgtagg ggaggggtggt gagaaggagg cagccaccca gtgggcgggg atctttcctg      60
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atccatccta agactgcagt tgctggccat taccagggat ctggcctctc atccagggtcc      180
ctcctccgct gctccgctgc cacagggcgg ggtctcccag tgccgggcag gcctgcagggt      240
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ctcctgctca aagctggagc ctgcttcctg tcgtccctgt cagcacctg ggtgggggag      360
ggaccaggta gtgggggaag tggaaaaggg attgagcggg tggagtgcag cagctgagaa      420
acagcagaag agaaatggag aaggatgacg acaagagacc aagagcatag gctgaaggac      480
cagaggggtg tgagaacaca ggggagatcc caggggctgc agaggctgca gaccctagac      540
tgtgagagcg agaccagagg cagagatgac cagagag      577

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&lt;210&gt; 401

&lt;211&gt; 574

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 401

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agccttgagg ggaggggtggt gagaaggagg cagccaccca gtgggcgggg atctttcctg      60
gtgactgaga attactgccc cttcacccca gggcctaatt tcccagtc ccacccact      120
atccatccta agactgcagt tgctggccat taccagggat ctggcctctc atccagggtcc      180
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aggggtgtga gaacacaggg gagatcccag gggctgcaga ggctgcagac cctagactgt      540
gagagcgaga ccagaggcag agatgaccag agag      574

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&lt;210&gt; 402

&lt;211&gt; 3053

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 402

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agcggggctg gggctccgct ggggaaccgg ccgagcggcg cgcgcggagg tgtccggcgg      60
ccaggaggat ggccaaggct ccgaagctgg aagacacctt cctgcaggcg cagcctgcgc      120

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438

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gccccgggga gaaaggcgaa gacccggagc tgccgggggc agtgaaatca cgaaatgcac	300
ttaaacaatg gtaacttttc ctctgaagaa gaggacgccg acaaccacga cagcaaaacc	360
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taccactccg tttattctgg aaagggttg acaagggtgg cttcactcgt aaatattcgc	780
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gaaaggggtg atttgaacag cattggctct caagccctc ttaccatttc aggagcaca	1140
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tggactgaac agcagctttc aagagacttc ttcagtggca gctgtgcggg gtctccatat	1860
aactcccggc caccgtctag ctatggccca tcctgcaag cccaggattc acacaatatg	1920
cagtttttaa atacaggaag cttcaatttc ttgagcaaca caggagctgc cagctgcca	1980

439

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tcaactgcccc cctacagtga catccacgat ccacttaaca ttttagatga cagtggtaga 2160
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<210> 403
<211> 619
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (70)..(167)
<223> n=a,c,g or t

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nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnntgt gaatgaagga 180
gagagtagag caaaataaat aaaaaatcag gggcccatct acatagggtg agatgcttgg 240
ttcatgttcc aagggtatcg gaagccacta tggcatttga gacgagtga agtttgatct 300
actcttcagc aatatcatc tggttgctct cggaagggtg agtgggtgaa acaaagggtg 360

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440

agatcatggg accagtcagg aggctgctgt gttgggtccag gagagaaaag atgggtggttt 420  
 gaactacaac cgtgaaagtg cagatggaaa gaggagggtg atgggggata tatttcggcg 480  
 gtagcactta agtgaaatgg agttttcttt gtgaaatatg tagaggaaat aatttctggg 540  
 agactagcaa gtgggaccaa atggagaaaa aatgattgtc tggtagacca tacagactca 600  
 aatttagact aggtatgtg 619

<210> 404  
 <211> 918  
 <212> DNA  
 <213> Homo sapien

<400> 404  
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 cagaagatca aggtgggaga cagagacaga gaaaacaaag gatttgatgg cttattagat 180  
 gtttgggaata ctttaaactt tattcatcct tgctttgctg tgtgcaactg tgtgcatggg 240  
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 gtgcagtgga ctctggggca gaggccttct cagtaaggca ggagaccag tccagaagcc 480  
 agcctaaggg aaaaccctaa tagatatgct tccaagtaaa aaaataataa taattctgtc 540  
 cagccaaatg acaagagact aggacaaaaa tatttaaaat tcacatggca gatacatttt 600  
 tataacaaaa aattggattc atgtaaagtc caaaatctaa atttcagaat aagaaatgaa 660  
 aacaggcgtg agccacctcg ccacgaggca tcaggcttct ttaaagttag agcacgcctg 720  
 tactagagca agcaggaatc agagaccttc cagaaatact actgtgtaag ggccagaaat 780  
 atcttcactt gtcattgtta tataatcatt attacttttg ctgtaatgtt aatattgatt 840  
 tattaatata tattatcttt tcatacatctt tctaagaaac atttatattg ataagatctt 900  
 ttattttgcc aagggtt 918

<210> 405  
 <211> 3085  
 <212> DNA  
 <213> Homo sapien

<400> 405  
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441

acctaagcaa taccattcag accatagggg tgggcaagga cttcatgact aaaacaccaa	180
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gcacagcaaa agaaactacc ataagagtga acaggcaact tacagaatgg gagaaaattt	300
ttgcaatctg cccatctgac aaagggtctaa tatccagaat ctacaaagaa gttaaacaaa	360
tttacaagaa aaagtcaaac aaccccatca aaaagtgggc aaaggatatg aacagacact	420
tctcacaaaga agacatttat gcagccaaca gacagatgaa aaaatgctca tcatcactgg	480
tcatcagaga aatgcaaagc aaaaccacaa tgagctggag cctgagtcg ctgcatggag	540
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tcagtcaaca cgatttctg tttgatgctg agaaagaaca tgagaaggct caggactgca	1740
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tcgacgtcat cgttggtgtt gttgttaaata ttaaaactcta tagcttttcc agaactgaga	1920
atgcaaaagt gaattatccc ctccacctct gaggtctttg cttttacctt tttctgtaag	1980



442

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aagaggagtg agaatcaaga gacctggggt ctaattaaat aactataaga taagagtggg 2160
gggtgtagct aaggctgggg ttcctttcct tactgtattt ttaccagata taacatctgg 2220
ctgtcacttc accatTTTTT gactctgttt actcatttag aataaaaaata gttaacattt 2280
actgggcata ccatatgtgc caagcactga gttactttat atacattagc tcatttaatt 2340
ctcaaaacct tagtaagtag acatagtatc tctatgtaac agatgtattt ccggaggcac 2400
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aaatatcaac ataacacaag gaaaggggca agccacaatg aagctctcaa tagcacattt 2820
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&lt;210&gt; 406

&lt;211&gt; 708

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (366)..(468)

&lt;223&gt; n=a,c,g or t

&lt;400&gt; 406

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443

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&lt;210&gt; 407

&lt;211&gt; 6087

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 407

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444

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445

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446

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&lt;210&gt; 408

&lt;211&gt; 79

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 408

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agtaaagat agatatttt 79

&lt;210&gt; 409

&lt;211&gt; 416

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

447

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<210> 410  
 <211> 76  
 <212> PRT  
 <213> Homo sapien

<400> 410

Met Ser Lys Phe Gln Gln Asn Asn Phe Ser Cys Lys Lys Ser Thr Thr  
 1 5 10 15

Gly Gln Asp Ala Val Gln Glu Asn Pro Arg Cys Val Glu Ser Asn Ile  
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Ser Trp Ser Ser Phe Ser Val Pro His Ser Ile Ser Tyr Ser Leu Thr  
 35 40 45

Thr Val Pro Val Ile Ser Thr Ser His Ser Arg His Glu Gly Trp Phe  
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Pro Cys Lys His Phe Gly Asp Cys Ala Pro Gly Arg  
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<210> 411  
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<400> 411

Met Phe Leu Ser Ile Leu Met Cys Arg Arg Lys Trp Val Met Val Leu  
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Ser Glu Ile Leu Asn Gly Ile Leu Lys Cys Val Ser Glu Phe Pro Ser  
 20 25 30

448

Thr Glu Leu Ile His Gly Tyr Leu Leu Ile Ile Asn Tyr Phe Lys Gln  
 35 40 45

His Lys Cys Leu Ser Leu Val Arg Leu Ser Phe Ser Lys His Ser Pro  
 50 55 60

Tyr Ser Val Val Leu Gln Cys Ser Ile Tyr Leu  
 65 70 75

<210> 412  
 <211> 854  
 <212> PRT  
 <213> Homo sapien

<400> 412

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
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Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

449

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp  
 210 215 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
 260 265 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
 275 280 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
 290 295 300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
 305 310 315 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His  
 325 330 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg  
 340 345 350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp  
 355 360 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile  
 370 375 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala  
 385 390 395 400

Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg



450  
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 Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu  
 420 425 430  
 Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr  
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 Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile  
 450 455 460  
 Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile  
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 Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala  
 485 490 495  
 Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys  
 500 505 510  
 Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn Ala Leu  
 515 520 525  
 Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His  
 530 535 540  
 Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu Leu Met  
 545 550 555 560  
 Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp  
 565 570 575  
 Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg Pro Glu  
 580 585 590  
 Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys  
 595 600 605  
 Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu Tyr Asp  
 610 615 620  
 Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu  
 625 630 635 640  
 Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu Glu Thr  
 645 650 655

451

Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met  
 660 665 670

Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys  
 675 680 685

Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile  
 690 695 700

Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn Asn Ile Gly Thr His  
 705 710 715 720

Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile  
 725 730 735

Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu  
 740 745 750

Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile Leu Val Ala Asp Ser  
 755 760 765

Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly Val Leu  
 770 775 780

Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu Ser Pro Ile Leu Pro  
 785 790 795 800

Ser Asp Ala Ala Lys Pro Phe Ser Val Val Val Phe His Cys Arg His  
 805 810 815

Met Phe His Lys Glu Cys Leu Pro Met Pro Ser Met Asn Ser Ala Ala  
 820 825 830

Gln Phe Cys Asn Ile Cys Ser Ala Lys Asn Arg Gly Pro Gly Ser Ala  
 835 840 845

Ile Leu Glu Met Lys Lys  
 850

<210> 413  
 <211> 392  
 <212> PRT  
 <213> Homo sapien

<400> 413

452

Met Ile Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr  
 1 5 10 15

Leu Ile Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val  
 20 25 30

Gln Ala Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu  
 35 40 45

Leu Lys Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn  
 50 55 60

Ala Leu Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu  
 65 70 75 80

Ile His Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu  
 85 90 95

Leu Met Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn  
 100 105 110

Glu Asp Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg  
 115 120 125

Pro Glu Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His  
 130 135 140

His Lys Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu  
 145 150 155 160

Tyr Asp Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys  
 165 170 175

Pro Leu Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu  
 180 185 190

Glu Thr Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu  
 195 200 205

Lys Met Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe  
 210 215 220

Ala Lys Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr  
 225 230 235 240

Ser Ile Asp Lys Pro Pro phe Ile Thr Gly Leu Leu Asn Asn Ile Gly

453

245                      250                      255

Thr His Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met  
260                                      265                                      270

Glu Ile Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr  
275                                      280                                      285

Asn Leu Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile Leu Val Ala  
290                                      295                                      300

Asp Ser Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly  
305                                      310                                      315                                      320

Val Leu Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu Ser Pro Ile  
325                                      330                                      335

Leu Pro Ser Asp Ala Ala Lys Pro Phe Ser Val Val Val Phe His Cys  
340                                      345                                      350

Arg His Met Phe His Lys Glu Cys Leu Pro Met Pro Ser Met Asn Ser  
355                                      360                                      365

Ala Ala Gln Phe Cys Asn Ile Cys Ser Ala Lys Asn Arg Gly Pro Gly  
370                                      375                                      380

Ser Ala Ile Leu Glu Met Lys Lys  
385                                      390

<210> 414  
<211> 802  
<212> PRT  
<213> Homo sapien

<400> 414

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
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Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
20                                      25                                      30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
35                                      40                                      45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
50                                      55                                      60

454

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp  
 210 215 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
 260 265 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
 275 280 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
 290 295 300

455

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
 305 310 315 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His  
 325 330 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg  
 340 345 350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp  
 355 360 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile  
 370 375 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala  
 385 390 395 400

Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg  
 405 410 415

Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu  
 420 425 430

Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr  
 435 440 445

Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile  
 450 455 460

Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile  
 465 470 475 480

Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala  
 485 490 495

Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys  
 500 505 510

Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn Ala Leu  
 515 520 525

Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His  
 530 535 540

Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu Leu Met

456

545		550		555		560
Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp						
		565		570		575
Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg Pro Glu						
		580		585		590
Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys						
		595		600		605
Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu Tyr Asp						
		610		615		620
Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu						
		625		630		635
						640
Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu Glu Thr						
		645		650		655
Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met						
		660		665		670
Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys						
		675		680		685
Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile						
		690		695		700
Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn Asn Ile Gly Thr His						
		705		710		715
						720
Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile						
		725		730		735
Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu						
		740		745		750
Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile Leu Val Ala Asp Ser						
		755		760		765
Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly Val Leu						
		770		775		780
Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu Ser Pro Ile Leu Pro						
		785		790		795
						800

457

Ser Glu

&lt;210&gt; 415

&lt;211&gt; 841

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 415

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
 1 5 10 15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190



458

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp  
 210 215 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
 260 265 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
 275 280 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
 290 295 300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
 305 310 315 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His  
 325 330 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg  
 340 345 350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp  
 355 360 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile  
 370 375 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala  
 385 390 395 400

Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg  
 405 410 415

Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu  
 420 425 430

Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr

459

435

440

445

Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile  
 450 455 460

Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile  
 465 470 475 480

Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala  
 485 490 495

Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys  
 500 505 510

Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn Ala Leu  
 515 520 525

Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His  
 530 535 540

Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu Leu Met  
 545 550 555 560

Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp  
 565 570 575

Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg Pro Glu  
 580 585 590

Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys  
 595 600 605

Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu Tyr Asp  
 610 615 620

Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu  
 625 630 635 640

Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu Glu Thr  
 645 650 655

Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met  
 660 665 670

Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys  
 675 680 685

460

Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile  
 690 695 700

Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn Asn Ile Gly Thr His  
 705 710 715 720

Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile  
 725 730 735

Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu  
 740 745 750

Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile Leu Val Ala Asp Ser  
 755 760 765

Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly Val Leu  
 770 775 780

Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu Ser Pro Ile Leu Pro  
 785 790 795 800

Ser Asp Ala Ala Lys Pro Phe Ser Val Val Val Phe His Cys Arg His  
 805 810 815

Met Phe His Lys Glu Cys Leu Pro Met Pro Ser Met Val Ser Trp Gln  
 820 825 830

Leu Gly Thr Tyr Gln Leu Glu Gly Asn  
 835 840

<210> 416

<211> 776

<212> PRT

<213> Homo sapien

<400> 416

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
 1 5 10 15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

461

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp  
 210 215 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
 260 265 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
 275 280 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu

462

290	295	300
Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp		
305	310	315 320
Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His		
	325	330 335
Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg		
	340	345 350
Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp		
	355	360 365
Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile		
	370	375 380
Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala		
	385	390 395 400
Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg		
	405	410 415
Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu		
	420	425 430
Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr		
	435	440 445
Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile		
	450	455 460
Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile		
	465	470 475 480
Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala		
	485	490 495
Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys		
	500	505 510
Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn Ala Leu		
	515	520 525
Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His		
	530	535 540

463

Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu Leu Met  
 545 550 555 560

Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp  
 565 570 575

Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg Pro Glu  
 580 585 590

Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys  
 595 600 605

Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu Tyr Asp  
 610 615 620

Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu  
 625 630 635 640

Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu Glu Thr  
 645 650 655

Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met  
 660 665 670

Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys  
 675 680 685

Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile  
 690 695 700

Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn Asn Ile Gly Thr His  
 705 710 715 720

Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile  
 725 730 735

Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu  
 740 745 750

Gln Gln Leu Leu Phe Phe Arg Met Leu Val Thr Ser Ile Glu Leu Glu  
 755 760 765

Leu Lys His Phe Leu Lys Asn Ser  
 770 775

464

<210> 417  
 <211> 415  
 <212> PRT  
 <213> Homo sapien

<400> 417

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
 1 5 10 15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp

465

210

215

220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
 260 265 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
 275 280 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
 290 295 300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
 305 310 315 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His  
 325 330 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg  
 340 345 350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp  
 355 360 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile  
 370 375 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala  
 385 390 395 400

Tyr Ile Asn His Leu Asp Ser Glu Val Arg Arg Gly Ser Ser Ile  
 405 410 415

&lt;210&gt; 418

&lt;211&gt; 346

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 418

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
 1 5 10 15



466

Asp Glu Ser Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp  
 210 215 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

467

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
                   260                  265                  270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
                   275                  280                  285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
                   290                  295                  300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
                   305                  310                  315                  320

Cys Asp Leu Gln Glu Phe Pro Ser Ile Arg Pro Pro Val Asp Phe Arg  
                   325                  330                  335

Leu Lys His Arg Tyr Ala Met His Ala Leu  
                   340                  345

&lt;210&gt; 419

&lt;211&gt; 158

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 419

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
   1                  5                  10                  15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
                   20                  25                  30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
                   35                  40                  45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
                   50                  55                  60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
   65                  70                  75                  80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
                   85                  90                  95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
                   100                  105                  110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
                   115                  120                  125

468

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Val Ser Ala Val Cys Leu Leu Pro  
 145 150 155

<210> 420

<211> 779

<212> PRT

<213> Homo sapien

<400> 420

Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr Gly Lys  
 1 5 10 15

Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe Asp Val  
 20 25 30

Val Gln Val Phe Gly Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe  
 35 40 45

Asp Cys Pro Ile Lys Ile Ile Ala Val His Pro His Phe Val Arg Ser  
 50 55 60

Ser Cys Lys Gln Phe Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu  
 65 70 75 80

Arg Ser Trp Met Asn Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu  
 85 90 95

Gly Asn Ile Arg Ser Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala  
 100 105 110

Asn Asn Met Gly Val Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile  
 115 120 125

Thr Asn Val Pro Arg Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro  
 130 135 140

Cys Ser Leu Cys Trp Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly  
 145 150 155 160

Thr Ser Val Lys Val Cys Ser Val Lys Glu Arg His Ala Ser Glu Met  
 165 170 175

469

Arg Asp Leu Pro Ser Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr  
 180 185 190

Glu Phe Tyr Ile Ser Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val  
 195 200 205

Leu Ser Tyr Val Lys Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys  
 210 215 220

Ala Arg Pro Arg Leu Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu  
 225 230 235 240

Glu Ile Ser Ser Asp Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu  
 245 250 255

Cys Arg Asp Tyr His Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr  
 260 265 270

Ile Val Ser Pro Arg Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp  
 275 280 285

Asp His Ile Asp Trp Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu  
 290 295 300

Met Ala Ala Glu Ile Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu  
 305 310 315 320

Asp Ile Gly Leu Ala Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr  
 325 330 335

Asp Ile Ala Ala Arg Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala  
 340 345 350

Leu Trp Glu Tyr Glu Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys  
 355 360 365

Ala Ile Ser Pro Tyr Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu  
 370 375 380

Ile Tyr Glu Met Ile Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly  
 385 390 395 400

Phe Ala Thr Leu Ile Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser  
 405 410 415

Val Ile Val Gln Ala Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn

470

420

425

430

Lys Thr Leu Leu Lys Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn  
 435 440 445

Tyr Gly Asn Ala Leu Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val  
 450 455 460

Phe Gln Leu Ile His Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys  
 465 470 475 480

Ile Val Leu Leu Met Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu  
 485 490 495

Leu Asp Asn Glu Asp Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu  
 500 505 510

Glu Asp Arg Pro Glu Leu Gln His Val Tyr Leu His Lys Leu Phe Lys  
 515 520 525

Arg Asp His His Lys Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu  
 530 535 540

Tyr Ala Glu Tyr Asp Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser  
 545 550 555 560

Thr His Cys Pro Leu Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn  
 565 570 575

Phe Val Glu Glu Thr Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg  
 580 585 590

Ser Ala Leu Lys Met Ile Met Glu Glu Leu His Asp Val Asp Lys Ala  
 595 600 605

Ile Glu Phe Ala Lys Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu  
 610 615 620

Ile Leu Tyr Ser Ile Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn  
 625 630 635 640

Asn Ile Gly Thr His Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys  
 645 650 655

Glu Gly Met Glu Ile Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu  
 660 665 670

471

Gln Asp Tyr Asn Leu Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile  
 675 680 685

Leu Val Ala Asp Ser Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln  
 690 695 700

Met Lys Gly Val Leu Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu  
 705 710 715 720

Ser Pro Ile Leu Pro Ser Asp Ala Ala Lys Pro Phe Ser Val Val Val  
 725 730 735

Phe His Cys Arg His Met Phe His Lys Glu Cys Leu Pro Met Pro Ser  
 740 745 750

Met Asn Ser Ala Ala Gln Phe Cys Asn Ile Cys Ser Ala Lys Asn Arg  
 755 760 765

Gly Pro Gly Ser Ala Ile Leu Glu Met Lys Lys  
 770 775

<210> 421

<211> 873

<212> PRT

<213> Homo sapien

<400> 421

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
 1 5 10 15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

472

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp  
 210 215 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
 260 265 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
 275 280 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
 290 295 300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
 305 310 315 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His  
 325 330 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg

473

340

345

350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp  
 355 360 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile  
 370 375 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala  
 385 390 395 400

Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg  
 405 410 415

Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu  
 420 425 430

Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr  
 435 440 445

Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile  
 450 455 460

Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile  
 465 470 475 480

Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala  
 485 490 495

Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys  
 500 505 510

Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn Ala Leu  
 515 520 525

Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His  
 530 535 540

Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu Leu Met  
 545 550 555 560

Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp  
 565 570 575

Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg Pro Glu  
 580 585 590



474

Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys  
 595 600 605

Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu Tyr Asp  
 610 615 620

Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu  
 625 630 635 640

Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu Glu Thr  
 645 650 655

Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met  
 660 665 670

Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys  
 675 680 685

Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile  
 690 695 700

Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn Asn Ile Gly Thr His  
 705 710 715 720

Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile  
 725 730 735

Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu  
 740 745 750

Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile Leu Val Ala Asp Ser  
 755 760 765

Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly Val Leu  
 770 775 780

Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu Ser Pro Ile Leu Pro  
 785 790 795 800

Ser Asp Ala Ala Lys Pro Phe Ser Val Val Val Phe His Cys Arg His  
 805 810 815

Met Phe His Lys Glu Cys Leu Pro Met Pro Ser Met Val Gly Thr Ala  
 820 825 830

475

Arg Ile His Leu Tyr Met Asp Phe Leu Leu Pro Leu Pro Pro Leu Arg  
 835 840 845

Arg Gln Asp Gln Ala Leu Pro Phe Leu Leu Leu Leu Ser Leu Leu Ser  
 850 855 860

Met Lys Thr Thr Glu Met Lys His Leu  
 865 870

<210> 422  
 <211> 826  
 <212> PRT  
 <213> Homo sapien

<400> 422

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
 1 5 10 15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser

476

165

170

175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp  
 210 215 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val  
 225 230 235 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser  
 245 250 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser  
 260 265 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys  
 275 280 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
 290 295 300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
 305 310 315 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His  
 325 330 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg  
 340 345 350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp  
 355 360 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile  
 370 375 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala  
 385 390 395 400

Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg  
 405 410 415

477

Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu  
 420 425 430

Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr  
 435 440 445

Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile  
 450 455 460

Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile  
 465 470 475 480

Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala  
 485 490 495

Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys  
 500 505 510

Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn Ala Leu  
 515 520 525

Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His  
 530 535 540

Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu Leu Met  
 545 550 555 560

Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp  
 565 570 575

Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg Pro Glu  
 580 585 590

Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys  
 595 600 605

Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu Tyr Asp  
 610 615 620

Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu  
 625 630 635 640

Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu Glu Thr  
 645 650 655

478

Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met  
660 665 670

Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys  
675 680 685

Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile  
690 695 700

Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn Asn Ile Gly Thr His  
705 710 715 720

Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile  
725 730 735

Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu  
740 745 750

Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile Leu Val Ala Asp Ser  
755 760 765

Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly Val Leu  
770 775 780

Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu Ser Pro Ile Leu Pro  
785 790 795 800

Ser Asp Ala Ala Glu Asn Asn Gly Thr Gly Lys Ser Cys Leu Leu Glu  
805 810 815

Lys Lys Leu Ile Pro Thr Ile Ser Leu Ala  
820 825

<210> 423

<211> 517

<212> PRT

<213> Homo sapien

<400> 423

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
1 5 10 15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala

479

35		40		45
Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr				
50		55		60
Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe				
65		70		75
Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly				
	85		90	95
Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly				
	100		105	110
Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys				
	115		120	125
Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe				
	130		135	140
Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn				
	145		150	155
Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser				
	165		170	175
Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val				
	180		185	190
Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg				
	195		200	205
Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp				
	210		215	220
Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val				
	225		230	235
Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser				
	245		250	255
Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser				
	260		265	270
Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys				
	275		280	285

480

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu  
 290 295 300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp  
 305 310 315 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His  
 325 330 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg  
 340 345 350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp  
 355 360 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile  
 370 375 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala  
 385 390 395 400

Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg  
 405 410 415

Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu  
 420 425 430

Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr  
 435 440 445

Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile  
 450 455 460

Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile  
 465 470 475 480

Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala  
 485 490 495

Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys  
 500 505 510

Thr Leu Ala Glu Leu  
 515

481

<210> 424  
 <211> 269  
 <212> PRT  
 <213> Homo sapien

<400> 424

Met Ala Glu Ala Glu Glu Gln Glu Thr Gly Ser Leu Glu Glu Ser Thr  
 1 5 10 15

Asp Glu Ser Glu Glu Glu Glu Ser Glu Glu Glu Pro Lys Leu Lys Tyr  
 20 25 30

Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala  
 35 40 45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr  
 50 55 60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe  
 65 70 75 80

Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly  
 85 90 95

Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly  
 100 105 110

Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys  
 115 120 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe  
 130 135 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn  
 145 150 155 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser  
 165 170 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val  
 180 185 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg  
 195 200 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp



482

210					215					220					
Lys	Asp	Asn	Val	Thr	Leu	Ile	Ile	Gly	Trp	Gly	Thr	Ser	Val	Lys	Val
225					230					235					240
Cys	Ser	Val	Lys	Glu	Arg	His	Ala	Ser	Glu	Met	Arg	Asp	Leu	Pro	Ser
				245					250					255	
Arg	Tyr	Val	Glu	Ile	Val	Ser	Ala	Asp	Pro	Val	Val	Lys			
			260					265							

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<210> 425
<211> 60
<212> PRT
<213> Homo sapien
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<400> 425

Met	Lys	Asn	Glu	Asn	Lys	Ala	Gln	Arg	Ser	Lys	Lys	Thr	Cys	Leu	Gln
1				5					10					15	
Glu	Ser	Ala	Ser	Glu	Asp	Gln	Gln	Glu	Thr	Glu	Asn	Leu	Gln	Asn	Ser
			20					25					30		
Leu	Leu	Ile	Gln	Lys	Ile	Ile	Gln	Asn	Ser	Thr	Met	Pro	Gln	Ser	Asp
		35					40					45			
Gln	Tyr	Lys	Phe	Glu	Val	Leu	Leu	Lys	Thr	Lys	Ala				
	50					55					60				

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<210> 426
<211> 96
<212> PRT
<213> Homo sapien
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<400> 426

Met	Thr	His	Tyr	Arg	Glu	Lys	His	Val	Ser	Gln	Glu	Cys	Ile	Gln	Ile
1				5					10					15	
Asp	Thr	Leu	Lys	Lys	His	Thr	Gly	Ile	Leu	Ala	Trp	Gly	Arg	Gly	Arg
			20					25					30		
Thr	Leu	Gly	Ile	Thr	Cys	Lys	Ile	Ile	Ser	Glu	Ser	Lys	Ile	Glu	Asn
		35					40					45			
His	Leu	Leu	Ser	His	Lys	Ala	Lys	Cys	His	Ser	Val	Arg	Glu	Met	Trp
	50					55					60				

483

Thr Glu Gln Arg Arg Leu Ala Gly Arg Cys Ser Gln Ala Pro Ser Ile  
 65 70 75 80

Asn His Thr Gln Cys Cys Leu His Leu Val Pro Gly Ser Gln Arg Leu  
 85 90 95

<210> 427  
 <211> 56  
 <212> PRT  
 <213> Homo sapien

<400> 427

Phe Trp Val Ala Gln Leu Leu Val Asn Gly Leu Ser Cys Glu Arg Gly  
 1 5 10 15

Pro Arg Val Asp Val Gln Gln Leu Ala Pro Pro Pro Pro Gln Gln  
 20 25 30

Pro Pro Gln Ala Pro Gln Ala Ala Gly Ala Ala Ala Thr Pro Ala Leu  
 35 40 45

Leu Phe Ile Phe Leu Ser Leu His  
 50 55

<210> 428  
 <211> 317  
 <212> PRT  
 <213> Homo sapien

<400> 428

Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly Gly  
 1 5 10 15

Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg Ser Pro  
 20 25 30

Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala Gly Ala Gly  
 35 40 45

Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala Arg Asp Gly Ser  
 50 55 60

Phe Thr Val Ser Ala Gln Lys Asn Val Glu His Gly Ile Ile Tyr Ile  
 65 70 75 80

Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe Met Gln Phe Ser Ser Leu  
 85 90 95

484

Glu His Glu Gly Glu Tyr Tyr Met Thr Pro Arg Asp Phe Leu Phe Ser  
 100 105 110

Val Met Phe Glu Gln Met Glu Arg Lys Thr Ser Val Lys Lys Leu Thr  
 115 120 125

Lys Lys Asp Ile Glu Asp Thr Leu Ser Gly Ile Gln Thr Ala Gly Cys  
 130 135 140

Gly Ser Thr Phe Phe Arg Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr  
 145 150 155 160

Thr Glu Tyr Leu Phe Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly  
 165 170 175

Phe His Val Ala Phe Lys Met Leu Asp Thr Asp Gly Asn Glu Met Ile  
 180 185 190

Glu Lys Arg Glu Phe Phe Lys Leu Gln Lys Ile Ile Ser Lys Gln Asp  
 195 200 205

Asp Leu Met Thr Val Lys Thr Asn Glu Thr Gly Tyr Gln Glu Ala Ile  
 210 215 220

Val Lys Glu Pro Glu Ile Asn Thr Thr Leu Gln Met Arg Phe Phe Gly  
 225 230 235 240

Lys Arg Gly Gln Arg Lys Leu His Tyr Lys Glu Phe Arg Arg Phe Met  
 245 250 255

Glu Asn Leu Gln Thr Glu Ile Gln Glu Met Glu Phe Leu Gln Phe Ser  
 260 265 270

Lys Gly Leu Ser Phe Met Arg Lys Glu Asp Phe Ala Glu Trp Leu Leu  
 275 280 285

Phe Phe Thr Asn Thr Glu Asn Lys Asp Ile Tyr Trp Lys Asn Val Arg  
 290 295 300

Glu Lys Leu Ser Ala Gly Glu Arg Ser Leu Arg Glu Leu  
 305 310 315

<210> 429

<211> 425

<212> PRT

<213> Homo sapien

485

&lt;400&gt; 429

Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly Gly  
 1 5 10 15

Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg Ser Pro  
 20 25 30

Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala Gly Ala Gly  
 35 40 45

Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala Arg Asp Gly Ser  
 50 55 60

Phe Thr Val Ser Ala Gln Lys Asn Val Glu His Gly Ile Ile Tyr Ile  
 65 70 75 80

Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe Met Gln Phe Ser Ser Leu  
 85 90 95

Glu His Glu Gly Glu Tyr Tyr Met Thr Pro Arg Asp Phe Leu Phe Ser  
 100 105 110

Val Met Phe Glu Gln Met Glu Arg Lys Thr Ser Val Lys Lys Leu Thr  
 115 120 125

Lys Lys Asp Ile Glu Asp Thr Leu Ser Gly Ile Gln Thr Ala Gly Cys  
 130 135 140

Gly Ser Thr Phe Phe Arg Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr  
 145 150 155 160

Thr Glu Tyr Leu Phe Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly  
 165 170 175

Phe His Val Ala Phe Lys Met Leu Asp Thr Asp Gly Asn Glu Met Ile  
 180 185 190

Glu Lys Arg Glu Phe Phe Lys Leu Gln Lys Ile Ile Ser Lys Gln Asp  
 195 200 205

Asp Leu Met Thr Val Lys Thr Asn Glu Thr Gly Tyr Gln Glu Ala Ile  
 210 215 220

Val Lys Glu Pro Glu Ile Asn Thr Thr Leu Gln Met Arg Phe Phe Gly  
 225 230 235 240

Lys Arg Gly Gln Arg Lys Leu His Tyr Lys Glu Phe Arg Arg Phe Met  
245 250 255

Lys Gly Leu Ser Phe Met Arg Lys Glu Asp Phe Ala Glu Trp Leu Leu  
275 280 285

Phe Phe Thr Asn Thr Glu Asn Lys Asp Ile Tyr Trp Lys Asn Val Arg  
290 295 300

Glu Lys Leu Ser Ala Gly Glu Ser Ile Ser Leu Asp Glu Phe Lys Ser  
305 310 315 320

Phe Cys His Phe Thr Thr His Leu Glu Asp Phe Ala Ile Ala Met Gln  
325 330 335

Met Phe Ser Leu Ala His Arg Pro Val Arg Leu Ala Glu Phe Lys Arg  
340 345 350

Ala Val Lys Val Ala Thr Gly Gln Glu Leu Ser Asn Asn Ile Leu Asp  
355 360 365

Thr Val Phe Lys Ile Phe Asp Leu Asp Gly Asp Glu Cys Leu Ser His  
370 375 380

Glu Glu Phe Leu Gly Val Leu Lys Asn Arg Met His Arg Gly Leu Trp  
385 390 395 400

Ser Pro Thr Phe Gln Gly Ser Glu Asn Trp Lys Gly Trp Arg Lys Glu  
405 410 415

Pro Leu Arg Arg Glu Gly Gly Asn Leu  
420 425

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<210> 430
<211> 327
<212> PRT
<213> Homo sapien
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<400> 430

Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly Gly  
1 5 10 15

487

Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg Ser Pro  
                   20                                  25                                  30

Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala Gly Ala Gly  
                   35                                  40                                  45

Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala Arg Asp Gly Ser  
                   50                                  55                                  60

Phe Thr Val Ser Ala Gln Lys Asn Val Glu His Gly Ile Ile Tyr Ile  
                   65                                  70                                  75                                  80

Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe Met Gln Phe Ser Ser Leu  
                                   85                                  90                                  95

Glu His Glu Gly Glu Tyr Tyr Met Thr Pro Arg Asp Phe Leu Phe Ser  
                                   100                                  105                                  110

Val Met Phe Glu Gln Met Glu Arg Lys Thr Ser Val Lys Lys Leu Thr  
                   115                                  120                                  125

Lys Lys Asp Ile Glu Asp Thr Leu Ser Gly Ile Gln Thr Ala Gly Cys  
                   130                                  135                                  140

Gly Ser Thr Phe Phe Arg Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr  
                   145                                  150                                  155                                  160

Thr Glu Tyr Leu Phe Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly  
                                   165                                  170                                  175

Phe His Val Ala Phe Lys Met Leu Asp Thr Asp Gly Asn Glu Met Ile  
                                   180                                  185                                  190

Glu Lys Arg Glu Phe Phe Lys Leu Gln Lys Ile Ile Ser Lys Gln Asp  
                   195                                  200                                  205

Asp Leu Met Thr Val Lys Thr Asn Glu Thr Gly Tyr Gln Glu Ala Ile  
                   210                                  215                                  220

Val Lys Glu Pro Glu Ile Asn Thr Thr Leu Gln Met Arg Phe Phe Gly  
                   225                                  230                                  235                                  240

Lys Arg Gly Gln Arg Lys Leu His Tyr Lys Glu Phe Arg Arg Phe Met  
                                   245                                  250                                  255

Glu Asn Leu Gln Thr Glu Ile Gln Glu Met Glu Phe Leu Gln Phe Ser

488

260

265

270

Lys Gly Leu Ser Phe Met Arg Lys Glu Asp Phe Ala Glu Trp Leu Leu  
 275 280 285

Phe Phe Thr Asn Thr Glu Asn Lys Asp Ile Tyr Trp Lys Asn Val Arg  
 290 295 300

Glu Lys Leu Ser Ala Gly Glu Val Gly Ile Pro Phe Tyr Tyr Ala Cys  
 305 310 315 320

Asp Lys Asp Glu Ile Ile Ser  
 325

<210> 431  
 <211> 203  
 <212> PRT  
 <213> Homo sapien

<400> 431

Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly Gly  
 1 5 10 15

Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg Ser Pro  
 20 25 30

Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala Gly Ala Gly  
 35 40 45

Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala Arg Asp Gly Ser  
 50 55 60

Phe Thr Val Ser Ala Gln Lys Asn Val Glu His Gly Ile Ile Tyr Ile  
 65 70 75 80

Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe Met Gln Phe Ser Ser Leu  
 85 90 95

Glu His Glu Gly Glu Tyr Tyr Met Thr Pro Arg Asp Phe Leu Phe Ser  
 100 105 110

Val Met Phe Glu Gln Met Glu Arg Lys Thr Ser Val Lys Lys Leu Thr  
 115 120 125

Lys Lys Asp Ile Glu Asp Thr Leu Ser Gly Ile Gln Thr Ala Gly Cys  
 130 135 140

489

Gly Ser Thr Phe Phe Arg Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr  
 145 150 155 160

Thr Glu Tyr Leu Phe Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly  
 165 170 175

Phe His Val Ala Phe Lys Met Leu Asp Thr Asp Gly Asn Glu Met Ile  
 180 185 190

Glu Lys Arg Glu Phe Phe Lys Val Ser Gly Arg  
 195 200

<210> 432  
 <211> 176  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> MISC\_FEATURE  
 <222> (36)..(36)  
 <223> x= any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (53)..(53)  
 <223> x= any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (58)..(58)  
 <223> x= any amino acid

<400> 432

Arg Thr Ala Gln Gln Gln Gln Lys Ser Asn Lys Thr Leu Val Gly Pro  
 1 5 10 15

Cys Gly Ala Leu Lys Ser Ser Ser Phe Phe Thr Ala Ser Ser Leu Ser  
 20 25 30

Val Asn Arg Xaa Arg Ile Ser Glu Asp Ser Phe Val Ile His Asn Gly  
 35 40 45

Gln Leu Val Asp Xaa Ile Ser Val Gly Xaa Lys Pro Phe Tyr Asp Arg  
 50 55 60

Met Ser Met Cys Trp Asp Ser Pro Ser Phe Gln Asp Gln Ile Lys Thr  
 65 70 75 80



490

Asp Val Arg Ala Ile Ile Gln Val Glu Val Tyr Leu Val Leu Lys Tyr  
85 90 95

Trp Leu Pro Phe Pro Gly Gly Met Ile Pro Cys Ser Thr Asn Ser Asn  
100 105 110

Asn Gly Ser Ser Ser Ser Leu Thr Ser Val Asn Leu Thr Phe Arg Ser  
115 120 125

Ser Ile Ser Ser Lys Ser Ser Gly Asp Ser Phe Arg Asn Ile Phe Ser  
130 135 140

Phe Ser Phe Thr Glu Thr Leu Ala Lys Ser Phe Ile Asp Pro Cys Leu  
145 150 155 160

Ser Leu Ile Tyr Leu Arg His Cys Ser Cys Arg Ile Arg His Glu Gly  
165 170 175

<210> 433

<211> 443

<212> PRT

<213> Homo sapien

<400> 433

Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly Gly  
1 5 10 15

Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg Ser Pro  
20 25 30

Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala Gly Ala Gly  
35 40 45

Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala Arg Asp Gly Ser  
50 55 60

Phe Thr Val Ser Ala Gln Lys Asn Val Glu His Gly Ile Ile Tyr Ile  
65 70 75 80

Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe Met Gln Phe Ser Ser Leu  
85 90 95

Glu His Glu Gly Glu Tyr Tyr Met Thr Pro Arg Asp Phe Leu Phe Ser  
100 105 110

Val Met Phe Glu Gln Met Glu Arg Lys Thr Ser Val Lys Lys Leu Thr

491

115	120	125
Lys Lys Asp Ile Glu Asp Thr Leu Ser Gly Ile Gln Thr Ala Gly Cys		
130	135	140
Gly Ser Thr Phe Phe Arg Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr		
145	150	155
Thr Glu Tyr Leu Phe Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly		
	165	170
Phe His Val Ala Phe Lys Met Leu Asp Thr Asp Gly Asn Glu Met Ile		
	180	185
Glu Lys Arg Glu Phe Phe Lys Asp Asp Thr Ile Asp Ser Glu Arg Gln		
195	200	205
Leu Gln Lys Ile Ile Ser Lys Gln Asp Asp Leu Met Thr Val Lys Thr		
210	215	220
Asn Glu Thr Gly Tyr Gln Glu Ala Ile Val Lys Glu Pro Glu Ile Asn		
225	230	235
Thr Thr Leu Gln Met Arg Phe Phe Gly Lys Arg Gly Gln Arg Lys Leu		
	245	250
His Tyr Lys Glu Phe Arg Arg Phe Met Glu Asn Leu Gln Thr Glu Ile		
	260	265
Gln Glu Met Glu Phe Leu Gln Phe Ser Lys Gly Leu Ser Phe Met Arg		
275	280	285
Lys Glu Asp Phe Ala Glu Trp Leu Leu Phe Phe Thr Asn Thr Glu Asn		
290	295	300
Lys Asp Ile Tyr Trp Lys Asn Val Arg Glu Lys Leu Ser Ala Gly Glu		
305	310	315
.Ser Ile Ser Leu Asp Glu Phe Lys Ser Phe Cys His Phe Thr Thr His		
	325	330
Leu Glu Asp Phe Ala Ile Ala Met Gln Met Phe Ser Leu Ala His Arg		
	340	345
Pro Val Arg Leu Ala Glu Phe Lys Arg Ala Val Lys Val Ala Thr Gly		
355	360	365

492

Gln Glu Leu Ser Asn Asn Ile Leu Asp Thr Val Phe Lys Ile Phe Asp  
 370 375 380

Leu Asp Gly Asp Glu Cys Leu Ser His Glu Glu Phe Leu Gly Val Leu  
 385 390 395 400

Lys Asn Arg Met His Arg Gly Leu Trp Val Pro Gln His Gln Ser Ile  
 405 410 415

Gln Glu Tyr Trp Lys Cys Val Lys Lys Glu Ser Ile Lys Gly Val Lys  
 420 425 430

Glu Val Trp Lys Gln Ala Gly Lys Gly Leu Phe  
 435 440

<210> 434

<211> 382

<212> PRT

<213> Homo sapien

<400> 434

Met Ala Ala Ala Ala Gly Ser Cys Ala Arg Val Ala Ala Trp Gly Gly  
 1 5 10 15

Lys Leu Arg Arg Gly Leu Ala Val Ser Arg Gln Ala Val Arg Ser Pro  
 20 25 30

Gly Pro Leu Ala Ala Ala Val Ala Gly Ala Ala Leu Ala Gly Ala Gly  
 35 40 45

Ala Ala Trp His His Ser Arg Val Ser Val Ala Ala Arg Asp Gly Ser  
 50 55 60

Phe Thr Val Ser Ala Gln Lys Asn Val Glu His Gly Ile Ile Tyr Ile  
 65 70 75 80

Gly Lys Pro Ser Leu Arg Lys Gln Arg Phe Met Gln Phe Ser Ser Leu  
 85 90 95

Glu His Glu Gly Glu Tyr Tyr Met Thr Pro Arg Asp Phe Leu Phe Ser  
 100 105 110

Val Met Phe Glu Gln Met Glu Arg Lys Thr Ser Val Lys Lys Leu Thr  
 115 120 125

493

Lys Lys Asp Ile Glu Asp Thr Leu Ser Gly Ile Gln Thr Ala Gly Cys  
 130 135 140

Gly Ser Thr Phe Phe Arg Asp Leu Gly Asp Lys Gly Leu Ile Ser Tyr  
 145 150 155 160

Thr Glu Tyr Leu Phe Leu Leu Thr Ile Leu Thr Lys Pro His Ser Gly  
 165 170 175

Phe His Val Ala Phe Lys Met Leu Asp Thr Asp Gly Asn Glu Met Ile  
 180 185 190

Glu Lys Arg Glu Phe Phe Lys Leu Gln Lys Ile Ile Ser Lys Gln Asp  
 195 200 205

Asp Leu Met Thr Val Lys Thr Asn Glu Thr Gly Tyr Gln Glu Ala Ile  
 210 215 220

Val Lys Glu Pro Glu Ile Asn Thr Thr Leu Gln Met Arg Phe Phe Gly  
 225 230 235 240

Lys Arg Gly Gln Arg Lys Leu His Tyr Lys Glu Phe Arg Arg Phe Met  
 245 250 255

Glu Asn Leu Gln Thr Glu Ile Gln Glu Met Glu Phe Leu Gln Phe Ser  
 260 265 270

Lys Gly Leu Ser Phe Met Arg Lys Glu Asp Phe Ala Glu Trp Leu Leu  
 275 280 285

Phe Phe Thr Asn Thr Glu Asn Lys Asp Ile Tyr Trp Lys Asn Val Arg  
 290 295 300

Glu Lys Leu Ser Ala Gly Glu Ser Ile Ser Leu Asp Glu Phe Lys Ser  
 305 310 315 320

Phe Cys His Phe Thr Thr His Leu Glu Asp Phe Ala Ile Ala Ile Ala  
 325 330 335

Lys Val Gln Leu Thr Tyr Met Ala Gly Arg Gln Arg Gly Val Lys Glu  
 340 345 350

Arg Trp Lys Gly His Thr Gly Arg Asp Leu Asn Asn Asn Leu Gly Asn  
 355 360 365

Gly Leu Lys Thr Leu Phe Gly Leu Glu Glu Ser Ala Lys Gln

494

370

375

380

<210> 435  
 <211> 53  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 435

Met Lys Pro Pro Ser Leu Leu Thr Cys His Asn Tyr Gln Gly Tyr Leu  
 1 5 10 15

Gln Lys Lys Val Lys Ala Lys Thr Ser Glu Val Glu Gly Ile Ile His  
 20 25 30

Phe Cys Ile Leu Ser Ser Gly Lys Ala Ile Glu Phe Lys Phe Asn Asn  
 35 40 45

Asn Asn Asn Asp Asp  
 50

<210> 436  
 <211> 59  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 436

Met Pro Phe Val Ile Val Thr Ile Ile Asn Ala Ile Thr Asp Phe His  
 1 5 10 15

Asp Ser Pro Ser Cys Pro Ile Tyr Cys Gln Ile Pro His Leu Pro Ile  
 20 25 30

Pro Glu Ala Met Leu Gly Gly Gln Gln Gln Thr Gln Asp Asn Leu Glu  
 35 40 45

Ser Trp Gly Val His His Ile Asp Glu His Val  
 50 55

<210> 437  
 <211> 24  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 437

Met Phe Gly Asp Gln Asn Lys Val Leu Phe Cys Met Asn Ser Cys Gln  
 1 5 10 15

Gly Ile Glu Leu Lys His Glu Lys

495

20

<210> 438  
 <211> 45  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 438

Met Pro Ala Asn Ser Thr Pro Ser Leu His Asn Phe Ser Val Leu Leu  
 1 5 10 15

Ser Leu His Phe Ile Tyr Cys Leu Glu Leu Phe Ala Asn Leu Tyr Lys  
 20 25 30

Leu Ile Phe Pro Tyr Pro Ser Ala Leu Tyr Thr Val Gly  
 35 40 45

<210> 439  
 <211> 112  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 439

Met Ser Glu Ala Ser Arg Leu Cys Ser Gly Tyr Tyr Ser Leu Asn Gln  
 1 5 10 15

Ser Phe Val Glu Pro Phe Gln Cys Pro Arg Arg Gly Glu Gly Ala Ala  
 20 25 30

Leu Gln Tyr Cys Cys Gly Phe Ala Asp Leu Lys Tyr Cys Cys Ser Glu  
 35 40 45

Pro Gly Ser Tyr Phe Pro Tyr Lys His Ser Tyr Met Trp Ser Leu Arg  
 50 55 60

Trp Ala Glu Ser Pro Arg Val Arg Arg Leu Ala Glu Pro Gly Ala Arg  
 65 70 75 80

Glu Ala Thr Ser Gly Ala Thr Pro Gly Pro Gly Arg Phe Pro Arg Val  
 85 90 95

Pro Ala Ile Arg Pro Arg Leu Gly Pro Tyr Gly Arg Thr Arg Ser Leu  
 100 105 110

<210> 440  
 <211> 15  
 <212> PRT  
 <213> Homo sapien

496

&lt;400&gt; 440

Met Leu Leu Lys Lys Asn Tyr Asn Leu Thr Ala Cys Leu Arg Arg  
1 5 10 15

&lt;210&gt; 441

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 441

Met Lys Ser Thr Ser Arg His Ala Ile Lys Lys Ser Tyr Asp Gln Pro  
1 5 10 15

Glu Lys Lys Tyr Arg Ser Ser Ser Asn Glu Gln Gln Leu  
20 25

&lt;210&gt; 442

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 442

Met Thr Asn Pro Gly Ser Asn Thr Tyr Gln Ser Gly Lys Ile Arg Thr  
1 5 10 15

Gln Asn Lys Glu Lys Leu Gly Pro Cys Thr Ile Ser Ala Thr Ile Lys  
20 25 30

Tyr Glu Tyr Thr Ser Glu Leu Ser Gly  
35 40

&lt;210&gt; 443

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 443

Met Val Thr Glu Ile Phe Gln Asn Ser Thr Leu His Asn Phe Asn Val  
1 5 10 15

Ser Thr His Glu His Lys His Leu Met Val Asn Leu  
20 25

&lt;210&gt; 444

&lt;211&gt; 121

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

497

&lt;400&gt; 444

Met Lys Ile Ala Thr Lys Lys Arg Asn Ser Val His Val Thr Phe Arg  
 1 5 10 15

Pro Ser Thr Glu Ser Val Gln Phe Tyr Asn Pro Leu Glu Asn Lys Glu  
 20 25 30

Ala Pro Trp Lys Met Arg Leu Arg Lys Leu Gly Gly Phe Ser Ser Gly  
 35 40 45

Ser Ser Asn Ser Ser Thr Ser Asn Thr His Thr Ser Thr Asn Ser Ala  
 50 55 60

Thr Glu Leu Val Lys Pro Gly Val Tyr Arg Pro Leu Asp Thr Leu Gly  
 65 70 75 80

Thr Ala Ser Val Ser Ser Lys Thr Val Lys Glu Ser Thr Glu Ile Pro  
 85 90 95

Thr Thr Ile Leu Gln Lys Glu Gly Ile Ala Ser Ser Gln Leu Gly Ser  
 100 105 110

Arg Ser Thr Leu Arg Ser Ser Ser His  
 115 120

&lt;210&gt; 445

&lt;211&gt; 955

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 445

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80



498

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
                                     85                                    90                                    95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
                                     100                                    105                                    110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
                                     115                                    120                                    125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
                                     130                                    135                                    140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
                                     145                                    150                                    155                                    160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
                                     165                                    170                                    175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
                                     180                                    185                                    190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
                                     195                                    200                                    205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
                                     210                                    215                                    220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
                                     225                                    230                                    235                                    240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
                                     245                                    250                                    255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
                                     260                                    265                                    270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
                                     275                                    280                                    285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
                                     290                                    295                                    300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
                                     305                                    310                                    315                                    320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn

499

325

330

335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

500

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
                   580                  585                  590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Ala Met  
                   595                  600                  605

Arg Ser Arg Ser Ile Gly Glu Cys Ala Leu Pro Ser Ala Tyr Ile Arg  
                   610                  615                  620

Ser Ala Lys Ser Ala Pro Val Leu Ile His Thr Ser Lys Pro Phe Leu  
                   625                  630                  635                  640

Pro Asp Ile Val Leu Thr Pro Leu Ser Asp Glu Leu Ser Asp Ile Asp  
                   645                  650                  655

Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser Gln  
                   660                  665                  670

Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu Gln  
                   675                  680                  685

Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe Thr  
                   690                  695                  700

Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu Pro  
                   705                  710                  715                  720

Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp Leu  
                   725                  730                  735

Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser Thr  
                   740                  745                  750

Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys Asp  
                   755                  760                  765

Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp Asp  
                   770                  775                  780

Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser Ser  
                   785                  790                  795                  800

Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe Gln  
                   805                  810                  815

501

Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr Gly  
                     820                    825                    830

Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln Ser  
                     835                    840                    845

Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp Ser  
                     850                    855                    860

Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala Thr  
                     865                    870                    875                    880

Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly Ser  
                     885                    890                    895

Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met Glu  
                     900                    905                    910

Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu Gln  
                     915                    920                    925

Thr Pro Asp Asp Leu Gly Asn Ile Ser Lys Leu Asp Ile Tyr Leu Phe  
                     930                    935                    940

Ser Phe Arg Ala Ser Val Ser Gly Asp His Lys  
                     945                    950                    955

<210> 446  
 <211> 1887  
 <212> PRT  
 <213> Homo sapien

<400> 446

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
   1                    5                    10                    15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
                     20                    25                    30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
                     35                    40                    45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
                     50                    55                    60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn

502

65		70		75		80									
Lys	Glu	Asn	Gln	Glu	Arg	Gly	Phe	Ser	Phe	Leu	Phe	Ser	His	Phe	Lys
				85					90					95	
Lys	Tyr	Tyr	Leu	Pro	Tyr	Ile	Phe	Pro	Asn	Ile	Cys	Lys	Glu	Asn	Ser
			100						105				110		
Leu	Tyr	His	Pro	Ile	Leu	Asp	Ile	Pro	Gln	Met	Arg	Pro	Lys	Pro	His
		115					120					125			
Tyr	Val	Val	Ile	Lys	Lys	Asp	Ala	Glu	Thr	Asn	Glu	Ala	Ile	Tyr	Cys
	130					135					140				
Thr	Lys	Glu	Pro	Phe	Ile	Lys	Ala	Arg	Val	Ile	Val	Ile	Arg	Trp	Leu
145					150					155					160
Val	Ser	Phe	Trp	Leu	Glu	Pro	Lys	Pro	His	Thr	Gly	Pro	His	Ile	Pro
				165					170					175	
Gly	Met	Glu	Gly	Glu	Val	Leu	Pro	Lys	Asn	Ile	Gln	Arg	Ala	Ala	Ala
			180						185				190		
Ser	Leu	Val	Ser	Arg	Glu	Glu	Ser	Lys	Asn	Asp	Asn	Ala	Asp	Lys	Thr
		195						200				205			
Asp	Arg	Thr	Thr	Glu	Pro	Glu	Gln	Ser	His	Ser	Asn	Thr	Ser	Thr	Leu
	210					215					220				
Thr	Glu	Arg	Glu	Pro	Ser	Ser	Ser	Ser	Leu	Cys	Ser	Ile	Asp	Glu	Glu
225				230						235					240
His	Leu	Thr	Asp	Ile	Glu	Ile	Val	Arg	Arg	Val	Phe	Ser	Ser	Lys	Arg
				245					250					255	
Ser	Asn	Val	Asn	Phe	Val	Thr	Glu	Ile	Phe	Arg	Gln	Ala	Phe	Leu	Leu
			260					265					270		
Pro	Ile	Cys	Glu	Ala	Ala	Ala	Met	Arg	Lys	Val	Val	Lys	Val	Tyr	Gln
		275					280					285			
Glu	Trp	Ile	Gln	Gln	Glu	Glu	Lys	Pro	Leu	Phe	Met	Gln	Glu	Pro	Glu
	290					295					300				
Glu	Ile	Val	Ile	Thr	Ser	Ser	Asp	Leu	Pro	Cys	Ile	Glu	Asn	Val	Thr
305					310					315				320	

503

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val	Ser	Val	Asp	Lys	Ser	Phe	Ser	Arg	Gly	Trp	Ser	Arg	Asp	Gln	Pro
				565					570					575	
Gly	Gln	Ala	Pro	Met	Arg	Gln	Arg	Ser	Ala	Thr	Thr	Thr	Gly	Ser	Pro
			580					585					590		
Gly	Thr	Glu	Lys	Ala	Arg	Ser	Ile	Val	Arg	Gln	Lys	Thr	Val	Asp	Ile
		595					600					605			
Asp	Asp	Ala	Gln	Ile	Leu	Pro	Arg	Ser	Thr	Arg	Val	Arg	His	Phe	Ser
	610					615					620				
Gln	Ser	Glu	Glu	Thr	Gly	Asn	Glu	Val	Phe	Gly	Ala	Leu	Asn	Glu	Glu
625					630					635					640
Gln	Pro	Leu	Pro	Arg	Ser	Ser	Ser	Thr	Ser	Asp	Ile	Leu	Glu	Pro	Phe
				645					650					655	
Thr	Val	Glu	Arg	Ala	Lys	Val	Asn	Lys	Glu	Asp	Met	Ser	Gln	Lys	Leu
			660					665					670		
Pro	Pro	Leu	Asn	Ser	Asp	Ile	Gly	Gly	Ser	Ser	Ala	Asn	Val	Pro	Asp
		675					680					685			
Leu	Met	Asp	Glu	Phe	Ile	Ala	Glu	Arg	Leu	Arg	Ser	Gly	Asn	Ala	Ser
	690					695					700				
Thr	Met	Thr	Arg	Arg	Gly	Ser	Ser	Pro	Gly	Ser	Leu	Glu	Ile	Pro	Lys
705					710					715					720
Asp	Leu	Pro	Asp	Ile	Leu	Asn	Lys	Gln	Asn	Gln	Met	Arg	Pro	Ile	Asp
				725					730					735	
Asp	Pro	Gly	Val	Pro	Ser	Glu	Trp	Thr	Ser	Pro	Ala	Ser	Ala	Gly	Ser
			740					745					750		
Ser	Asp	Leu	Ile	Ser	Ser	Asp	Ser	His	Ser	Asp	Ser	Phe	Ser	Ala	Phe
		755					760					765			
Gln	Tyr	Asp	Gly	Arg	Lys	Phe	Asp	Asn	Phe	Gly	Phe	Gly	Thr	Asp	Thr
	770					775					780				
Gly	Val	Thr	Ser	Ser	Ala	Asp	Val	Asp	Ser	Gly	Ser	Gly	His	His	Gln
785					790					795					800

505

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 820 825 830

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
 835 840 845

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
 850 855 860

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
 865 870 875 880

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
 885 890 895

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
 900 905 910

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
 915 920 925

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
 930 935 940

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
 945 950 955 960

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
 965 970 975

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
 980 985 990

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
 995 1000 1005

Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe  
 1010 1015 1020

Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile  
 1025 1030 1035

Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu



506

1040		1045		1050
Gly Leu Pro Gly Ala Thr Met	Leu Ile Met Asp Phe	Ile Val Ala		
1055	1060	1065		
Ala Gly Arg Val Ala Ser Ser	Ala Phe Leu Asn Ala	Pro Arg Val		
1070	1075	1080		
Glu Ala Gln Val Leu Leu Gly	Ser Leu Val Cys Phe	Pro Asn Leu		
1085	1090	1095		
Tyr Cys Glu Leu Pro Ser Leu	His Pro Asn Ile Pro	Asp Val Ala		
1100	1105	1110		
Val Ser Gln Phe Thr Asp Val	Lys Glu Leu Ile Ile	Lys Thr Val		
1115	1120	1125		
Leu Ser Ser Ala Arg Asp Glu	Pro Ser Gly Pro Ala	Arg Cys Val		
1130	1135	1140		
Ala Leu Cys Ser Leu Gly Ile	Trp Ile Cys Glu Glu	Leu Val His		
1145	1150	1155		
Glu Ser His His Pro Gln Ile	Lys Glu Ala Leu Asn	Val Ile Cys		
1160	1165	1170		
Val Ser Leu Lys Phe Thr Asn	Lys Thr Val Ala His	Val Ala Cys		
1175	1180	1185		
Asn Met Leu His Met Leu Val	His Tyr Val Pro Arg	Leu Gln Ile		
1190	1195	1200		
Tyr Gln Pro Asp Ser Pro Leu	Lys Ile Ile Gln Ile	Leu Ile Ala		
1205	1210	1215		
Thr Ile Thr His Leu Leu Pro	Ser Thr Glu Ala Ser	Ser Tyr Glu		
1220	1225	1230		
Met Asp Lys Arg Leu Val Val	Ser Leu Leu Leu Cys	Leu Leu Asp		
1235	1240	1245		
Trp Ile Met Ala Leu Pro Leu	Lys Thr Leu Leu Gln	Pro Phe His		
1250	1255	1260		
Ala Thr Gly Ala Glu Ser Asp	Lys Thr Glu Lys Ser	Val Leu Asn		
1265	1270	1275		

507

Cys Ile Tyr Lys Val Leu His	Gly Cys Val Tyr Gly	Ala Gln Cys
1280	1285	1290
Phe Ser Asn Pro Arg Tyr Phe	Pro Met Ser Leu Ser	Asp Leu Ala
1295	1300	1305
Ser Val Asp Tyr Asp Pro Phe	Met His Leu Glu Ser	Leu Lys Glu
1310	1315	1320
Pro Glu Pro Leu His Ser Pro	Asp Ser Glu Arg Ser	Ser Lys Leu
1325	1330	1335
Gln Pro Val Thr Glu Val Lys	Thr Gln Met Gln His	Gly Leu Ile
1340	1345	1350
Ser Ile Ala Ala Arg Thr Val	Ile Thr His Leu Val	Asn His Leu
1355	1360	1365
Gly His Tyr Pro Met Ser Gly	Gly Pro Ala Met Leu	Thr Ser Gln
1370	1375	1380
Val Cys Glu Asn His Asp Asn	His Tyr Ser Glu Ser	Thr Glu Leu
1385	1390	1395
Ser Pro Glu Leu Phe Glu Ser	Pro Asn Ile Gln Phe	Phe Val Leu
1400	1405	1410
Asn Asn Thr Thr Leu Val Ser	Cys Ile Gln Ile Arg	Ser Glu Glu
1415	1420	1425
Asn Met Pro Gly Gly Gly Leu	Ser Ala Gly Leu Ala	Ser Ala Asn
1430	1435	1440
Ser Asn Val Arg Ile Ile Val	Arg Asp Leu Ser Gly	Lys Tyr Ser
1445	1450	1455
Trp Asp Ser Ala Ile Leu Tyr	Gly Pro Pro Pro Val	Ser Gly Leu
1460	1465	1470
Ser Glu Pro Thr Ser Phe Met	Leu Ser Leu Ser His	Gln Glu Lys
1475	1480	1485
Pro Glu Glu Pro Pro Thr Ser	Asn Glu Cys Leu Glu	Asp Ile Thr
1490	1495	1500



509

Val Ile Phe His Val Ser Thr Arg Met Pro Ser Asp Ser Asp Asp  
 1730 1735 1740

Ser Leu Thr Lys Lys Leu Arg His Leu Gly Asn Asp Glu Val His  
 1745 1750 1755

Ile Val Trp Ser Glu His Thr Arg Asp Tyr Arg Arg Gly Ile Ile  
 1760 1765 1770

Pro Thr Glu Phe Gly Asp Val Leu Ile Val Ile Tyr Pro Met Lys  
 1775 1780 1785

Asn His Met Phe Ser Ile Gln Ile Met Lys Lys Pro Glu Val Pro  
 1790 1795 1800

Phe Phe Gly Pro Leu Phe Asp Gly Ala Ile Val Asn Gly Lys Val  
 1805 1810 1815

Leu Pro Ile Met Val Arg Ala Thr Ala Ile Asn Ala Ser Arg Ala  
 1820 1825 1830

Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Phe Tyr Glu Glu Arg  
 1835 1840 1845

Ala Arg Tyr Leu Gln Thr Ile Val Gln His His Leu Glu Pro Thr  
 1850 1855 1860

Thr Phe Glu Asp Phe Ala Ala Gln Val Phe Ser Pro Ala Pro Tyr  
 1865 1870 1875

His His Leu Pro Ser Asp Ala Asp His  
 1880 1885

<210> 447

<211> 1455

<212> PRT

<213> Homo sapien

<400> 447

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 1 5 10 15

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 20 25 30

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 35 40 45

510

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 50 55 60

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 65 70 75 80

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 85 90 95

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 100 105 110

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 115 120 125

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 130 135 140

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 145 150 155 160

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 165 170 175

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 180 185 190

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 195 200 205

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 210 215 220

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 225 230 235 240

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 245 250 255

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 260 265 270

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 275 280 285

511

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 290 295 300

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 305 310 315 320

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 325 330 335

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 340 345 350

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 355 360 365

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 370 375 380

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 385 390 395 400

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
 405 410 415

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
 420 425 430

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
 435 440 445

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
 450 455 460

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
 465 470 475 480

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
 485 490 495

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
 500 505 510

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
 515 520 525

512

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
 530 535 540

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
 545 550 555 560

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
 565 570 575

Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe Tyr  
 580 585 590

Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile Val Asn  
 595 600 605

Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu Gly Leu Pro  
 610 615 620

Gly Ala Thr Met Leu Ile Met Asp Phe Ile Val Ala Ala Gly Arg Val  
 625 630 635 640

Ala Ser Ser Ala Phe Leu Asn Ala Pro Arg Val Glu Ala Gln Val Leu  
 645 650 655

Leu Gly Ser Leu Val Cys Phe Pro Asn Leu Tyr Cys Glu Leu Pro Ser  
 660 665 670

Leu His Pro Asn Ile Pro Asp Val Ala Val Ser Gln Phe Thr Asp Val  
 675 680 685

Lys Glu Leu Ile Ile Lys Thr Val Leu Ser Ser Ala Arg Asp Glu Pro  
 690 695 700

Ser Gly Pro Ala Arg Cys Val Ala Leu Cys Ser Leu Gly Ile Trp Ile  
 705 710 715 720

Cys Glu Glu Leu Val His Glu Ser His His Pro Gln Ile Lys Glu Ala  
 725 730 735

Leu Asn Val Ile Cys Val Ser Leu Lys Phe Thr Asn Lys Thr Val Ala  
 740 745 750

His Val Ala Cys Asn Met Leu His Met Leu Val His Tyr Val Pro Arg  
 755 760 765

Leu Gln Ile Tyr Gln Pro Asp Ser Pro Leu Lys Ile Ile Gln Ile Leu

513

770

775

780

Ile Ala Thr Ile Thr His Leu Leu Pro Ser Thr Glu Ala Ser Ser Tyr  
 785 790 795 800

Glu Met Asp Lys Arg Leu Val Val Ser Leu Leu Leu Cys Leu Leu Asp  
 805 810 815

Trp Ile Met Ala Leu Pro Leu Lys Thr Leu Leu Gln Pro Phe His Ala  
 820 825 830

Thr Gly Ala Glu Ser Asp Lys Thr Glu Lys Ser Val Leu Asn Cys Ile  
 835 840 845

Tyr Lys Val Leu His Gly Cys Val Tyr Gly Ala Gln Cys Phe Ser Asn  
 850 855 860

Pro Arg Tyr Phe Pro Met Ser Leu Ser Asp Leu Ala Ser Val Asp Tyr  
 865 870 875 880

Asp Pro Phe Met His Leu Glu Ser Leu Lys Glu Pro Glu Pro Leu His  
 885 890 895

Ser Pro Asp Ser Glu Arg Ser Ser Lys Leu Gln Pro Val Thr Glu Val  
 900 905 910

Lys Thr Gln Met Gln His Gly Leu Ile Ser Ile Ala Ala Arg Thr Val  
 915 920 925

Ile Thr His Leu Val Asn His Leu Gly His Tyr Pro Met Ser Gly Gly  
 930 935 940

Pro Ala Met Leu Thr Ser Gln Val Cys Glu Asn His Asp Asn His Tyr  
 945 950 955 960

Ser Glu Ser Thr Glu Leu Ser Pro Glu Leu Phe Glu Ser Pro Asn Ile  
 965 970 975

Gln Phe Phe Val Leu Asn Asn Thr Thr Leu Val Ser Cys Ile Gln Ile  
 980 985 990

Arg Ser Glu Glu Asn Met Pro Gly Gly Gly Leu Ser Ala Gly Leu Ala  
 995 1000 1005

Ser Ala Asn Ser Asn Val Arg Ile Ile Val Arg Asp Leu Ser Gly  
 1010 1015 1020



514

Lys	Tyr	Ser	Trp	Asp	Ser	Ala	Ile	Leu	Tyr	Gly	Pro	Pro	Pro	Val
1025						1030					1035			
Ser	Gly	Leu	Ser	Glu	Pro	Thr	Ser	Phe	Met	Leu	Ser	Leu	Ser	His
1040						1045					1050			
Gln	Glu	Lys	Pro	Glu	Glu	Pro	Pro	Thr	Ser	Asn	Glu	Cys	Leu	Glu
1055						1060					1065			
Asp	Ile	Thr	Val	Lys	Asp	Gly	Leu	Ser	Leu	Gln	Phe	Lys	Arg	Phe
1070						1075					1080			
Arg	Glu	Thr	Val	Pro	Thr	Trp	Asp	Thr	Ile	Arg	Asp	Glu	Glu	Asp
1085						1090					1095			
Val	Leu	Asp	Glu	Leu	Leu	Gln	Tyr	Leu	Gly	Val	Thr	Ser	Pro	Glu
1100						1105					1110			
Cys	Leu	Gln	Arg	Thr	Gly	Ile	Ser	Leu	Asn	Ile	Pro	Ala	Pro	Gln
1115						1120					1125			
Pro	Val	Cys	Ile	Ser	Glu	Lys	Gln	Glu	Asn	Asp	Val	Ile	Asn	Ala
1130						1135					1140			
Ile	Leu	Lys	Gln	His	Thr	Glu	Glu	Lys	Glu	Phe	Val	Glu	Lys	His
1145						1150					1155			
Phe	Asn	Asp	Leu	Asn	Met	Lys	Ala	Val	Glu	Gln	Asp	Glu	Pro	Ile
1160						1165					1170			
Pro	Gln	Lys	Pro	Gln	Ser	Ala	Phe	Tyr	Tyr	Cys	Arg	Leu	Leu	Leu
1175						1180					1185			
Ser	Ile	Leu	Gly	Met	Asn	Ser	Trp	Asp	Lys	Arg	Arg	Ser	Phe	His
1190						1195					1200			
Leu	Leu	Lys	Lys	Asn	Glu	Lys	Leu	Leu	Arg	Glu	Leu	Arg	Asn	Leu
1205						1210					1215			
Asp	Ser	Arg	Gln	Cys	Arg	Glu	Thr	His	Lys	Ile	Ala	Val	Phe	Tyr
1220						1225					1230			
Val	Ala	Glu	Gly	Gln	Glu	Asp	Lys	His	Ser	Ile	Leu	Thr	Asn	Thr
1235						1240					1245			

515

Gly Gly Ser Gln Ala Tyr Glu Asp Phe Val Ala Gly Leu Gly Trp  
 1250 1255 1260  
  
 Glu Val Asn Leu Thr Asn His Cys Gly Phe Met Gly Gly Leu Gln  
 1265 1270 1275  
  
 Lys Asn Lys Ser Thr Gly Leu Thr Thr Pro Tyr Phe Ala Thr Ser  
 1280 1285 1290  
  
 Thr Val Glu Val Ile Phe His Val Ser Thr Arg Met Pro Ser Asp  
 1295 1300 1305  
  
 Ser Asp Asp Ser Leu Thr Lys Lys Leu Arg His Leu Gly Asn Asp  
 1310 1315 1320  
  
 Glu Val His Ile Val Trp Ser Glu His Thr Arg Asp Tyr Arg Arg  
 1325 1330 1335  
  
 Gly Ile Ile Pro Thr Glu Phe Gly Asp Val Leu Ile Val Ile Tyr  
 1340 1345 1350  
  
 Pro Met Lys Asn His Met Phe Ser Ile Gln Ile Met Lys Lys Pro  
 1355 1360 1365  
  
 Glu Val Pro Phe Phe Gly Pro Leu Phe Asp Gly Ala Ile Val Asn  
 1370 1375 1380  
  
 Gly Lys Val Leu Pro Ile Met Val Arg Ala Thr Ala Ile Asn Ala  
 1385 1390 1395  
  
 Ser Arg Ala Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Phe Tyr  
 1400 1405 1410  
  
 Glu Glu Arg Ala Arg Tyr Leu Gln Thr Ile Val Gln His His Leu  
 1415 1420 1425  
  
 Glu Pro Thr Thr Phe Glu Asp Phe Ala Ala Gln Val Phe Ser Pro  
 1430 1435 1440  
  
 Ala Pro Tyr His His Leu Pro Ser Asp Ala Asp His  
 1445 1450 1455

&lt;210&gt; 448

&lt;211&gt; 1771

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

516

&lt;400&gt; 448

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Arg Ala Ala Ala Ser Leu Val Ser  
 65 70 75 80

Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr Asp Arg Thr Thr  
 85 90 95

Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu Thr Glu Arg Glu  
 100 105 110

Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu His Leu Thr Asp  
 115 120 125

Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg Ser Asn Val Asn  
 130 135 140

Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu Pro Ile Cys Glu  
 145 150 155 160

Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln Glu Trp Ile Gln  
 165 170 175

Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu Glu Ile Val Ile  
 180 185 190

Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr Asp His Asp Ile  
 195 200 205

Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn Gly Thr Asn Thr  
 210 215 220

Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn Gly Ser Tyr Gln  
 225 230 235 240

Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu Gln Asn Ile Arg  
245 250 255

Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile Asn Ser Ser Asn  
260 265 270

Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn Leu Leu Asp Glu  
275 280 285

His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr Arg Tyr Met Val  
290 295 300

Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln Met Leu Leu Val  
305 310 315 320

Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro Ser Gln Ala Phe  
325 330 335

Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala Gly Arg Leu Ala  
340 345 350

Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile Lys Ala Asn Leu  
355 360 365

Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu Leu Ser Val Leu  
370 375 380

Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu Trp Ser Leu Thr  
385 390 395 400

Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu Tyr Ser Leu Asp  
405 410 415

Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln Lys Gln Lys Lys  
420 425 430

His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys Val Ser Val Asp  
435 440 445

Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro Gly Gln Ala Pro  
450 455 460

Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro Gly Thr Glu Lys  
465 470 475 480

518

Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile Asp Asp Ala Gln  
 485 490 495

Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser Gln Ser Glu Glu  
 500 505 510

Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu Gln Pro Leu Pro  
 515 520 525

Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe Thr Val Glu Arg  
 530 535 540

Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu Pro Pro Leu Asn  
 545 550 555 560

Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp Leu Met Asp Glu  
 565 570 575

Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser Thr Met Thr Arg  
 580 585 590

Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys Asp Leu Pro Asp  
 595 600 605

Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp Asp Pro Gly Val  
 610 615 620

Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser Ser Asp Leu Ile  
 625 630 635 640

Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe Gln Tyr Asp Gly  
 645 650 655

Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr Gly Val Thr Ser  
 660 665 670

Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln Ser Ala Glu Glu  
 675 680 685

Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp Ser Glu Thr Ser  
 690 695 700

Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala Thr Ile Thr Gly  
 705 710 715 720

519

Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly Ser Arg Ser Gln  
                               725                              730                              735

Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met Glu Gln Lys Asp  
                               740                              745                              750

Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu Gln Thr Pro Asp  
                               755                              760                              765

Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys Ser Val Met Ala  
                               770                              775                              780

Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala Thr Val Met Trp  
                               785                              790                              795                              800

Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser Ile Met Asp Pro  
                               805                              810                              815

Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu Leu Trp Gln Asn  
                               820                              825                              830

Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr Asp Asn Leu Thr  
                               835                              840                              845

Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg Ile Leu Thr Pro  
                               850                              855                              860

Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr Lys Gln Gly Lys  
                               865                              870                              875                              880

Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys Arg Arg Gln Asp  
                               885                              890                              895

Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe Tyr Asn Ile Met His  
                               900                              905                              910

Cys Gly Leu Leu His Ile Asp Gln Asp Ile Val Asn Thr Ile Ile Lys  
                               915                              920                              925

His Cys Ser Pro Gln Phe Phe Ser Leu Gly Leu Pro Gly Ala Thr Met  
                               930                              935                              940

Leu Ile Met Asp Phe Ile Val Ala Ala Gly Arg Val Ala Ser Ser Ala  
                               945                              950                              955                              960

Phe Leu Asn Ala Pro Arg Val Glu Ala Gln Val Leu Leu Gly Ser Leu

520

965

970

975

Val Cys Phe Pro Asn Leu Tyr Cys Glu Leu Pro Ser Leu His Pro Asn  
 980 985 990

Ile Pro Asp Val Ala Val Ser Gln Phe Thr Asp Val Lys Glu Leu Ile  
 995 1000 1005

Ile Lys Thr Val Leu Ser Ser Ala Arg Asp Glu Pro Ser Gly Pro  
 1010 1015 1020

Ala Arg Cys Val Ala Leu Cys Ser Leu Gly Ile Trp Ile Cys Glu  
 1025 1030 1035

Glu Leu Val His Glu Ser His His Pro Gln Ile Lys Glu Ala Leu  
 1040 1045 1050

Asn Val Ile Cys Val Ser Leu Lys Phe Thr Asn Lys Thr Val Ala  
 1055 1060 1065

His Val Ala Cys Asn Met Leu His Met Leu Val His Tyr Val Pro  
 1070 1075 1080

Arg Leu Gln Ile Tyr Gln Pro Asp Ser Pro Leu Lys Ile Ile Gln  
 1085 1090 1095

Ile Leu Ile Ala Thr Ile Thr His Leu Leu Pro Ser Thr Glu Ala  
 1100 1105 1110

Ser Ser Tyr Glu Met Asp Lys Arg Leu Val Val Ser Leu Leu Leu  
 1115 1120 1125

Cys Leu Leu Asp Trp Ile Met Ala Leu Pro Leu Lys Thr Leu Leu  
 1130 1135 1140

Gln Pro Phe His Ala Thr Gly Ala Glu Ser Asp Lys Thr Glu Lys  
 1145 1150 1155

Ser Val Leu Asn Cys Ile Tyr Lys Val Leu His Gly Cys Val Tyr  
 1160 1165 1170

Gly Ala Gln Cys Phe Ser Asn Pro Arg Tyr Phe Pro Met Ser Leu  
 1175 1180 1185

Ser Asp Leu Ala Ser Val Asp Tyr Asp Pro Phe Met His Leu Glu  
 1190 1195 1200

521

Ser	Leu	Lys	Glu	Pro	Glu	Pro	Leu	His	Ser	Pro	Asp	Ser	Glu	Arg
1205						1210					1215			
Ser	Ser	Lys	Leu	Gln	Pro	Val	Thr	Glu	Val	Lys	Thr	Gln	Met	Gln
1220						1225					1230			
His	Gly	Leu	Ile	Ser	Ile	Ala	Ala	Arg	Thr	Val	Ile	Thr	His	Leu
1235						1240					1245			
Val	Asn	His	Leu	Gly	His	Tyr	Pro	Met	Ser	Gly	Gly	Pro	Ala	Met
1250						1255					1260			
Leu	Thr	Ser	Gln	Val	Cys	Glu	Asn	His	Asp	Asn	His	Tyr	Ser	Glu
1265						1270					1275			
Ser	Thr	Glu	Leu	Ser	Pro	Glu	Leu	Phe	Glu	Ser	Pro	Asn	Ile	Gln
1280						1285					1290			
Phe	Phe	Val	Leu	Asn	Asn	Thr	Thr	Leu	Val	Ser	Cys	Ile	Gln	Ile
1295						1300					1305			
Arg	Ser	Glu	Glu	Asn	Met	Pro	Gly	Gly	Gly	Leu	Ser	Ala	Gly	Leu
1310						1315					1320			
Ala	Ser	Ala	Asn	Ser	Asn	Val	Arg	Ile	Ile	Val	Arg	Asp	Leu	Ser
1325						1330					1335			
Gly	Lys	Tyr	Ser	Trp	Asp	Ser	Ala	Ile	Leu	Tyr	Gly	Pro	Pro	Pro
1340						1345					1350			
Val	Ser	Gly	Leu	Ser	Glu	Pro	Thr	Ser	Phe	Met	Leu	Ser	Leu	Ser
1355						1360					1365			
His	Gln	Glu	Lys	Pro	Glu	Glu	Pro	Pro	Thr	Ser	Asn	Glu	Cys	Leu
1370						1375					1380			
Glu	Asp	Ile	Thr	Val	Lys	Asp	Gly	Leu	Ser	Leu	Gln	Phe	Lys	Arg
1385						1390					1395			
Phe	Arg	Glu	Thr	Val	Pro	Thr	Trp	Asp	Thr	Ile	Arg	Asp	Glu	Glu
1400						1405					1410			
Asp	Val	Leu	Asp	Glu	Leu	Leu	Gln	Tyr	Leu	Gly	Val	Thr	Ser	Pro
1415						1420					1425			



522

Glu Cys	Leu Gln Arg Thr Gly	Ile Ser Leu Asn Ile	Pro Ala Pro
1430	1435	1440	
Gln Pro	Val Cys Ile Ser Glu	Lys Gln Glu Asn Asp	Val Ile Asn
1445	1450	1455	
Ala Ile	Leu Lys Gln His Thr	Glu Glu Lys Glu Phe	Val Glu Lys
1460	1465	1470	
His Phe	Asn Asp Leu Asn Met	Lys Ala Val Glu Gln	Asp Glu Pro
1475	1480	1485	
Ile Pro	Gln Lys Pro Gln Ser	Ala Phe Tyr Tyr Cys	Arg Leu Leu
1490	1495	1500	
Leu Ser	Ile Leu Gly Met Asn	Ser Trp Asp Lys Arg	Arg Ser Phe
1505	1510	1515	
His Leu	Leu Lys Lys Asn Glu	Lys Leu Leu Arg Glu	Leu Arg Asn
1520	1525	1530	
Leu Asp	Ser Arg Gln Cys Arg	Glu Thr His Lys Ile	Ala Val Phe
1535	1540	1545	
Tyr Val	Ala Glu Gly Gln Glu	Asp Lys His Ser Ile	Leu Thr Asn
1550	1555	1560	
Thr Gly	Gly Ser Gln Ala Tyr	Glu Asp Phe Val Ala	Gly Leu Gly
1565	1570	1575	
Trp Glu	Val Asn Leu Thr Asn	His Cys Gly Phe Met	Gly Gly Leu
1580	1585	1590	
Gln Lys	Asn Lys Ser Thr Gly	Leu Thr Thr Pro Tyr	Phe Ala Thr
1595	1600	1605	
Ser Thr	Val Glu Val Ile Phe	His Val Ser Thr Arg	Met Pro Ser
1610	1615	1620	
Asp Ser	Asp Asp Ser Leu Thr	Lys Lys Leu Arg His	Leu Gly Asn
1625	1630	1635	
Asp Glu	Val His Ile Val Trp	Ser Glu His Thr Arg	Asp Tyr Arg
1640	1645	1650	

523

Arg Gly Ile Ile Pro Thr Glu Phe Gly Asp Val Leu Ile Val Ile  
 1655 1660 1665

Tyr Pro Met Lys Asn His Met Phe Ser Ile Gln Ile Met Lys Lys  
 1670 1675 1680

Pro Glu Val Pro Phe Phe Gly Pro Leu Phe Asp Gly Ala Ile Val  
 1685 1690 1695

Asn Gly Lys Val Leu Pro Ile Met Val Arg Ala Thr Ala Ile Asn  
 1700 1705 1710

Ala Ser Arg Ala Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Phe  
 1715 1720 1725

Tyr Glu Glu Arg Ala Arg Tyr Leu Gln Thr Ile Val Gln His His  
 1730 1735 1740

Leu Glu Pro Thr Thr Phe Glu Asp Phe Ala Ala Gln Val Phe Ser  
 1745 1750 1755

Pro Ala Pro Tyr His His Leu Pro Ser Asp Ala Asp His  
 1760 1765 1770

<210> 449  
 <211> 1403  
 <212> PRT  
 <213> Homo sapien

<400> 449

Met Lys Ile Ala Thr Lys Lys Arg Asn Ser Val His Val Thr Phe Arg  
 1 5 10 15

Pro Ser Thr Glu Ser Val Gln Phe Tyr Asn Pro Leu Glu Asn Lys Glu  
 20 25 30

Ala Pro Trp Lys Met Arg Leu Arg Lys Leu Gly Gly Phe Ser Ser Gly  
 35 40 45

Ser Ser Asn Ser Ser Thr Ser Asn Thr His Thr Ser Thr Asn Ser Ala  
 50 55 60

Thr Glu Leu Val Lys Pro Gly Val Tyr Arg Pro Leu Asp Thr Leu Gly  
 65 70 75 80

Thr Ala Ser Val Ser Ser Lys Thr Val Lys Glu Ser Thr Glu Ile Pro  
 85 90 95

524

Thr Thr Ile Leu Gln Lys Glu Gly Ile Ala Ser Ser Gln Leu Gly Ser  
 100 105 110

Arg Ser Thr Leu Arg Ser Ser Ser His Glu Ala Gly Leu Gln Gln Gly  
 115 120 125

Ser Leu Gly Gly Val Tyr Lys Thr Val Val His Ala Leu Ser Lys Pro  
 130 135 140

Lys Ala Asn Val Ser Pro Gln Arg Gln Asn Arg Met Pro Pro Glu Ala  
 145 150 155 160

Pro Leu Arg Asp Leu Tyr Ser His Val Met Gly Tyr Phe Gly Arg Lys  
 165 170 175

Ala Ala Val Asn Lys Glu Asp Met Ser Gln Lys Leu Pro Pro Leu Asn  
 180 185 190

Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp Leu Met Asp Glu  
 195 200 205

Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser Thr Met Thr Arg  
 210 215 220

Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys Asp Leu Pro Asp  
 225 230 235 240

Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp Asp Pro Gly Val  
 245 250 255

Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser Ser Asp Leu Ile  
 260 265 270

Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe Gln Tyr Asp Gly  
 275 280 285

Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr Gly Val Thr Ser  
 290 295 300

Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln Ser Ala Glu Glu  
 305 310 315 320

Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp Ser Glu Thr Ser  
 325 330 335

525

Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala Thr Ile Thr Gly  
 340 345 350

Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly Ser Arg Ser Gln  
 355 360 365

Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met Glu Gln Lys Asp  
 370 375 380

Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu Gln Thr Pro Asp  
 385 390 395 400

Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys Ser Val Met Ala  
 405 410 415

Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala Thr Val Met Trp  
 420 425 430

Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser Ile Met Asp Pro  
 435 440 445

Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu Leu Trp Gln Asn  
 450 455 460

Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr Asp Asn Leu Thr  
 465 470 475 480

Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg Ile Leu Thr Pro  
 485 490 495

Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr Lys Gln Gly Lys  
 500 505 510

Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys Arg Arg Gln Asp  
 515 520 525

Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe Tyr Asn Ile Met His  
 530 535 540

Cys Gly Leu Leu His Ile Asp Gln Asp Ile Val Asn Thr Ile Ile Lys  
 545 550 555 560

His Cys Ser Pro Gln Phe Phe Ser Leu Gly Leu Pro Gly Ala Thr Met  
 565 570 575

526

Leu Ile Met Asp Phe Ile Val Ala Ala Gly Arg Val Ala Ser Ser Ala  
 580 585 590

Phe Leu Asn Ala Pro Arg Val Glu Ala Gln Val Leu Leu Gly Ser Leu  
 595 600 605

Val Cys Phe Pro Asn Leu Tyr Cys Glu Leu Pro Ser Leu His Pro Asn  
 610 615 620

Ile Pro Asp Val Ala Val Ser Gln Phe Thr Asp Val Lys Glu Leu Ile  
 625 630 635 640

Ile Lys Thr Val Leu Ser Ser Ala Arg Asp Glu Pro Ser Gly Pro Ala  
 645 650 655

Arg Cys Val Ala Leu Cys Ser Leu Gly Ile Trp Ile Cys Glu Glu Leu  
 660 665 670

Val His Glu Ser His His Pro Gln Ile Lys Glu Ala Leu Asn Val Ile  
 675 680 685

Cys Val Ser Leu Lys Phe Thr Asn Lys Thr Val Ala His Val Ala Cys  
 690 695 700

Asn Met Leu His Met Leu Val His Tyr Val Pro Arg Leu Gln Ile Tyr  
 705 710 715 720

Gln Pro Asp Ser Pro Leu Lys Ile Ile Gln Ile Leu Ile Ala Thr Ile  
 725 730 735

Thr His Leu Leu Pro Ser Thr Glu Ala Ser Ser Tyr Glu Met Asp Lys  
 740 745 750

Arg Leu Val Val Ser Leu Leu Leu Cys Leu Leu Asp Trp Ile Met Ala  
 755 760 765

Leu Pro Leu Lys Thr Leu Leu Gln Pro Phe His Ala Thr Gly Ala Glu  
 770 775 780

Ser Asp Lys Thr Glu Lys Ser Val Leu Asn Cys Ile Tyr Lys Val Leu  
 785 790 795 800

His Gly Cys Val Tyr Gly Ala Gln Cys Phe Ser Asn Pro Arg Tyr Phe  
 805 810 815

Pro Met Ser Leu Ser Asp Leu Ala Ser Val Asp Tyr Asp Pro Phe Met

527

820

825

830

His Leu Glu Ser Leu Lys Glu Pro Glu Pro Leu His Ser Pro Asp Ser  
 835 840 845

Glu Arg Ser Ser Lys Leu Gln Pro Val Thr Glu Val Lys Thr Gln Met  
 850 855 860

Gln His Gly Leu Ile Ser Ile Ala Ala Arg Thr Val Ile Thr His Leu  
 865 870 875 880

Val Asn His Leu Gly His Tyr Pro Met Ser Gly Gly Pro Ala Met Leu  
 885 890 895

Thr Ser Gln Val Cys Glu Asn His Asp Asn His Tyr Ser Glu Ser Thr  
 900 905 910

Glu Leu Ser Pro Glu Leu Phe Glu Ser Pro Asn Ile Gln Phe Phe Val  
 915 920 925

Leu Asn Asn Thr Thr Leu Val Ser Cys Ile Gln Ile Arg Ser Glu Glu  
 930 935 940

Asn Met Pro Gly Gly Gly Leu Ser Ala Gly Leu Ala Ser Ala Asn Ser  
 945 950 955 960

Asn Val Arg Ile Ile Val Arg Asp Leu Ser Gly Lys Tyr Ser Trp Asp  
 965 970 975

Ser Ala Ile Leu Tyr Gly Pro Pro Pro Val Ser Gly Leu Ser Glu Pro  
 980 985 990

Thr Ser Phe Met Leu Ser Leu Ser His Gln Glu Lys Pro Glu Glu Pro  
 995 1000 1005

Pro Thr Ser Asn Glu Cys Leu Glu Asp Ile Thr Val Lys Asp Gly  
 1010 1015 1020

Leu Ser Leu Gln Phe Lys Arg Phe Arg Glu Thr Val Pro Thr Trp  
 1025 1030 1035

Asp Thr Ile Arg Asp Glu Glu Asp Val Leu Asp Glu Leu Leu Gln  
 1040 1045 1050

Tyr Leu Gly Val Thr Ser Pro Glu Cys Leu Gln Arg Thr Gly Ile  
 1055 1060 1065

Ser	Leu	Asn	Ile	Pro	Ala	Pro	Gln	Pro	Val	Cys	Ile	Ser	Glu	Lys
1070						1075					1080			
Gln	Glu	Asn	Asp	Val	Ile	Asn	Ala	Ile	Leu	Lys	Gln	His	Thr	Glu
1085						1090					1095			
Glu	Lys	Glu	Phe	Val	Glu	Lys	His	Phe	Asn	Asp	Leu	Asn	Met	Lys
1100						1105					1110			
Ala	Val	Glu	Gln	Asp	Glu	Pro	Ile	Pro	Gln	Lys	Pro	Gln	Ser	Ala
1115						1120					1125			
Phe	Tyr	Tyr	Cys	Arg	Leu	Leu	Leu	Ser	Ile	Leu	Gly	Met	Asn	Ser
1130						1135					1140			
Trp	Asp	Lys	Arg	Arg	Ser	Phe	His	Leu	Leu	Lys	Lys	Asn	Glu	Lys
1145						1150					1155			
Leu	Leu	Arg	Glu	Leu	Arg	Asn	Leu	Asp	Ser	Arg	Gln	Cys	Arg	Glu
1160						1165					1170			
Thr	His	Lys	Ile	Ala	Val	Phe	Tyr	Val	Ala	Glu	Gly	Gln	Glu	Asp
1175						1180					1185			
Lys	His	Ser	Ile	Leu	Thr	Asn	Thr	Gly	Gly	Ser	Gln	Ala	Tyr	Glu
1190						1195					1200			
Asp	Phe	Val	Ala	Gly	Leu	Gly	Trp	Glu	Val	Asn	Leu	Thr	Asn	His
1205						1210					1215			
Cys	Gly	Phe	Met	Gly	Gly	Leu	Gln	Lys	Asn	Lys	Ser	Thr	Gly	Leu
1220						1225					1230			
Thr	Thr	Pro	Tyr	Phe	Ala	Thr	Ser	Thr	Val	Glu	Val	Ile	Phe	His
1235						1240					1245			
Val	Ser	Thr	Arg	Met	Pro	Ser	Asp	Ser	Asp	Asp	Ser	Leu	Thr	Lys
1250						1255					1260			
Lys	Leu	Arg	His	Leu	Gly	Asn	Asp	Glu	Val	His	Ile	Val	Trp	Ser
1265						1270					1275			
Glu	His	Thr	Arg	Asp	Tyr	Arg	Arg	Gly	Ile	Ile	Pro	Thr	Glu	Phe
1280						1285					1290			

529

Gly Asp Val Leu Ile Val Ile Tyr Pro Met Lys Asn His Met Phe  
 1295 1300 1305

Ser Ile Gln Ile Met Lys Lys Pro Glu Val Pro Phe Phe Gly Pro  
 1310 1315 1320

Leu Phe Asp Gly Ala Ile Val Asn Gly Lys Val Leu Pro Ile Met  
 1325 1330 1335

Val Arg Ala Thr Ala Ile Asn Ala Ser Arg Ala Leu Lys Ser Leu  
 1340 1345 1350

Ile Pro Leu Tyr Gln Asn Phe Tyr Glu Glu Arg Ala Arg Tyr Leu  
 1355 1360 1365

Gln Thr Ile Val Gln His His Leu Glu Pro Thr Thr Phe Glu Asp  
 1370 1375 1380

Phe Ala Ala Gln Val Phe Ser Pro Ala Pro Tyr His His Leu Pro  
 1385 1390 1395

Ser Asp Ala Asp His  
 1400

<210> 450  
 <211> 1909  
 <212> PRT  
 <213> Homo sapien

<400> 450

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys



530

85

90

95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

531

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

532

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 675 680 685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 755 760 765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

533

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
                     820                    825                    830

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
                     835                    840                    845

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
                     850                    855                    860

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
                     865                    870                    875                    880

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
                     885                    890                    895

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
                     900                    905                    910

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
                     915                    920                    925

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
                     930                    935                    940

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
                     945                    950                    955                    960

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
                     965                    970                    975

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
                     980                    985                    990

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
                     995                    1000                    1005

Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe  
                     1010                    1015                    1020

Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile  
                     1025                    1030                    1035

Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu  
                     1040                    1045                    1050

Gly Leu Pro Gly Ala Thr Met Leu Ile Met Asp Phe Ile Val Ala

534

1055		1060		1065
Ala Gly Arg Val Ala Ser Ser	Ala Phe Leu Asn Ala	Pro Arg Val		
1070	1075	1080		
Glu Ala Gln Val Leu Leu Gly	Ser Leu Val Cys Phe	Pro Asn Leu		
1085	1090	1095		
Tyr Cys Glu Leu Pro Ser Leu	His Pro Asn Ile Pro	Asp Val Ala		
1100	1105	1110		
Val Ser Gln Phe Thr Asp Val	Lys Glu Leu Ile Ile	Lys Thr Val		
1115	1120	1125		
Leu Ser Ser Ala Arg Asp Glu	Pro Ser Gly Pro Ala	Arg Cys Val		
1130	1135	1140		
Ala Leu Cys Ser Leu Gly Ile	Trp Ile Cys Glu Glu	Leu Val His		
1145	1150	1155		
Glu Ser His His Pro Gln Ile	Lys Glu Ala Leu Asn	Val Ile Cys		
1160	1165	1170		
Val Ser Leu Lys Phe Thr Asn	Lys Thr Val Ala His	Val Ala Cys		
1175	1180	1185		
Asn Met Leu His Met Leu Val	His Tyr Val Pro Arg	Leu Gln Ile		
1190	1195	1200		
Tyr Gln Pro Asp Ser Pro Leu	Lys Ile Ile Gln Ile	Leu Ile Ala		
1205	1210	1215		
Thr Ile Thr His Leu Leu Pro	Ser Thr Glu Ala Ser	Ser Tyr Glu		
1220	1225	1230		
Met Asp Lys Arg Leu Val Val	Ser Leu Leu Leu Cys	Leu Leu Asp		
1235	1240	1245		
Trp Ile Met Ala Leu Pro Leu	Lys Thr Leu Leu Gln	Pro Phe His		
1250	1255	1260		
Ala Thr Gly Ala Glu Ser Asp	Lys Thr Glu Lys Ser	Val Leu Asn		
1265	1270	1275		
Cys Ile Tyr Lys Val Leu His	Gly Cys Val Tyr Gly	Ala Gln Cys		
1280	1285	1290		

535

Phe Ser Asn Pro Arg Tyr Phe Pro Met Ser Leu Ser Asp Leu Ala	1295	1300	1305
Ser Val Asp Tyr Asp Pro Phe Met His Leu Glu Ser Leu Lys Glu	1310	1315	1320
Pro Glu Pro Leu His Ser Pro Asp Ser Glu Arg Ser Ser Lys Leu	1325	1330	1335
Gln Pro Val Thr Glu Val Lys Thr Gln Met Gln His Gly Leu Ile	1340	1345	1350
Ser Ile Ala Ala Arg Thr Val Ile Thr His Leu Val Asn His Leu	1355	1360	1365
Gly His Tyr Pro Met Ser Gly Gly Pro Ala Met Leu Thr Ser Gln	1370	1375	1380
Val Cys Glu Asn His Asp Asn His Tyr Ser Glu Ser Thr Glu Leu	1385	1390	1395
Ser Pro Glu Leu Phe Glu Ser Pro Asn Ile Gln Phe Phe Val Leu	1400	1405	1410
Asn Asn Thr Thr Leu Val Ser Cys Ile Gln Ile Arg Ser Glu Glu	1415	1420	1425
Asn Met Pro Gly Gly Gly Leu Ser Ala Gly Leu Ala Ser Ala Asn	1430	1435	1440
Ser Asn Val Arg Ile Ile Val Arg Asp Leu Ser Gly Lys Tyr Ser	1445	1450	1455
Trp Asp Ser Ala Ile Leu Tyr Gly Pro Pro Pro Val Ser Gly Leu	1460	1465	1470
Ser Glu Pro Thr Ser Phe Met Leu Ser Leu Ser His Gln Glu Lys	1475	1480	1485
Pro Glu Glu Pro Pro Thr Ser Asn Glu Cys Leu Glu Asp Ile Thr	1490	1495	1500
Val Lys Asp Gly Leu Ser Leu Gln Phe Lys Arg Phe Arg Glu Thr	1505	1510	1515

536

Val	Pro	Thr	Trp	Asp	Thr	Ile	Arg	Asp	Glu	Glu	Asp	Val	Leu	Asp
1520						1525					1530			
Glu	Leu	Leu	Gln	Tyr	Leu	Gly	Val	Thr	Ser	Pro	Glu	Cys	Leu	Gln
1535						1540					1545			
Arg	Thr	Gly	Ile	Ser	Leu	Asn	Ile	Pro	Ala	Pro	Gln	Pro	Val	Cys
1550						1555					1560			
Ile	Ser	Glu	Lys	Gln	Glu	Asn	Asp	Val	Ile	Asn	Ala	Ile	Leu	Lys
1565						1570					1575			
Gln	His	Thr	Glu	Glu	Lys	Glu	Phe	Val	Glu	Lys	His	Phe	Asn	Asp
1580						1585					1590			
Leu	Asn	Met	Lys	Ala	Val	Glu	Gln	Asp	Glu	Pro	Ile	Pro	Gln	Lys
1595						1600					1605			
Pro	Gln	Ser	Ala	Phe	Tyr	Tyr	Cys	Arg	Leu	Leu	Leu	Ser	Ile	Leu
1610						1615					1620			
Gly	Met	Asn	Ser	Trp	Asp	Lys	Arg	Arg	Ser	Phe	His	Leu	Leu	Lys
1625						1630					1635			
Lys	Asn	Glu	Lys	Leu	Leu	Arg	Glu	Leu	Arg	Asn	Leu	Asp	Ser	Arg
1640						1645					1650			
Gln	Cys	Arg	Glu	Thr	His	Lys	Ile	Ala	Val	Phe	Tyr	Val	Ala	Glu
1655						1660					1665			
Gly	Gln	Glu	Asp	Lys	His	Ser	Ile	Leu	Thr	Asn	Thr	Gly	Gly	Ser
1670						1675					1680			
Gln	Ala	Tyr	Glu	Asp	Phe	Val	Ala	Gly	Leu	Gly	Trp	Glu	Val	Asn
1685						1690					1695			
Leu	Thr	Asn	His	Cys	Gly	Phe	Met	Gly	Gly	Leu	Gln	Lys	Asn	Lys
1700						1705					1710			
Ser	Thr	Gly	Leu	Thr	Thr	Pro	Tyr	Phe	Ala	Thr	Ser	Thr	Val	Glu
1715						1720					1725			
Val	Ile	Phe	His	Val	Ser	Thr	Arg	Met	Pro	Ser	Asp	Ser	Asp	Asp
1730						1735					1740			

537

Ser Leu Thr Lys Lys Ile Gln Val Tyr Asp Thr Tyr Val Phe Leu  
 1745 1750 1755

Leu Ser Glu Glu Leu Val Leu Thr Phe Leu Glu Glu Leu Arg His  
 1760 1765 1770

Leu Gly Asn Asp Glu Val His Ile Val Trp Ser Glu His Thr Arg  
 1775 1780 1785

Asp Tyr Arg Arg Gly Ile Ile Pro Thr Glu Phe Gly Asp Val Leu  
 1790 1795 1800

Ile Val Ile Tyr Pro Met Lys Asn His Met Phe Ser Ile Gln Ile  
 1805 1810 1815

Met Lys Lys Pro Glu Val Pro Phe Phe Gly Pro Leu Phe Asp Gly  
 1820 1825 1830

Ala Ile Val Asn Gly Lys Val Leu Pro Ile Met Val Arg Ala Thr  
 1835 1840 1845

Ala Ile Asn Ala Ser Arg Ala Leu Lys Ser Leu Ile Pro Leu Tyr  
 1850 1855 1860

Gln Asn Phe Tyr Glu Glu Arg Ala Arg Tyr Leu Gln Thr Ile Val  
 1865 1870 1875

Gln His His Leu Glu Pro Thr Thr Phe Glu Asp Phe Ala Ala Gln  
 1880 1885 1890

Val Phe Ser Pro Ala Pro Tyr His His Leu Pro Ser Asp Ala Asp  
 1895 1900 1905

His

<210> 451  
 <211> 1704  
 <212> PRT  
 <213> Homo sapien

<400> 451

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30



538

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

539

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

540

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 675 680 685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe

541

755

760

765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 820 825 830

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
 835 840 845

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
 850 855 860

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
 865 870 875 880

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
 885 890 895

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
 900 905 910

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
 915 920 925

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
 930 935 940

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
 945 950 955 960

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
 965 970 975

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
 980 985 990

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
 995 1000 1005

542

Arg	Arg	Gln	Asp	Val	Ser	Pro	Asn	Arg	Asp	Phe	Leu	Thr	His	Phe
1010						1015					1020			
Tyr	Asn	Ile	Met	His	Cys	Gly	Leu	Leu	His	Ile	Asp	Gln	Asp	Ile
1025						1030					1035			
Val	Asn	Thr	Ile	Ile	Lys	His	Cys	Ser	Pro	Gln	Phe	Phe	Ser	Leu
1040						1045					1050			
Gly	Leu	Pro	Gly	Ala	Thr	Met	Leu	Ile	Met	Asp	Phe	Ile	Val	Ala
1055						1060					1065			
Ala	Gly	Arg	Val	Ala	Ser	Ser	Ala	Phe	Leu	Asn	Ala	Pro	Arg	Val
1070						1075					1080			
Glu	Ala	Gln	Val	Leu	Leu	Gly	Ser	Leu	Val	Cys	Phe	Pro	Asn	Leu
1085						1090					1095			
Tyr	Cys	Glu	Leu	Pro	Ser	Leu	His	Pro	Asn	Ile	Pro	Asp	Val	Ala
1100						1105					1110			
Val	Ser	Gln	Phe	Thr	Asp	Val	Lys	Glu	Leu	Ile	Ile	Lys	Thr	Val
1115						1120					1125			
Leu	Ser	Ser	Ala	Arg	Asp	Glu	Pro	Ser	Gly	Pro	Ala	Arg	Cys	Val
1130						1135					1140			
Ala	Leu	Cys	Ser	Leu	Gly	Ile	Trp	Ile	Cys	Glu	Glu	Leu	Val	His
1145						1150					1155			
Glu	Ser	His	His	Pro	Gln	Ile	Lys	Glu	Ala	Leu	Asn	Val	Ile	Cys
1160						1165					1170			
Val	Ser	Leu	Lys	Phe	Thr	Asn	Lys	Thr	Val	Ala	His	Val	Ala	Cys
1175						1180					1185			
Asn	Met	Leu	His	Met	Leu	Val	His	Tyr	Val	Pro	Arg	Leu	Gln	Ile
1190						1195					1200			
Tyr	Gln	Pro	Asp	Ser	Pro	Leu	Lys	Ile	Ile	Gln	Ile	Leu	Ile	Ala
1205						1210					1215			
Thr	Ile	Thr	His	Leu	Leu	Pro	Ser	Thr	Glu	Ala	Ser	Ser	Tyr	Glu
1220						1225					1230			

543

Met	Asp	Lys	Arg	Leu	Val	Val	Ser	Leu	Leu	Leu	Cys	Leu	Leu	Asp
1235						1240					1245			
Trp	Ile	Met	Ala	Leu	Pro	Leu	Lys	Thr	Leu	Leu	Gln	Pro	Phe	His
1250						1255					1260			
Ala	Thr	Gly	Ala	Glu	Ser	Asp	Lys	Thr	Glu	Lys	Ser	Val	Leu	Asn
1265						1270					1275			
Cys	Ile	Tyr	Lys	Val	Leu	His	Gly	Cys	Val	Tyr	Gly	Ala	Gln	Cys
1280						1285					1290			
Phe	Ser	Asn	Pro	Arg	Tyr	Phe	Pro	Met	Ser	Leu	Ser	Asp	Leu	Ala
1295						1300					1305			
Ser	Val	Asp	Tyr	Asp	Pro	Phe	Met	His	Leu	Glu	Ser	Leu	Lys	Glu
1310						1315					1320			
Pro	Glu	Pro	Leu	His	Ser	Pro	Asp	Ser	Glu	Arg	Ser	Ser	Lys	Leu
1325						1330					1335			
Gln	Pro	Val	Thr	Glu	Val	Lys	Thr	Gln	Met	Gln	His	Gly	Leu	Ile
1340						1345					1350			
Ser	Ile	Ala	Ala	Arg	Thr	Val	Ile	Thr	His	Leu	Val	Asn	His	Leu
1355						1360					1365			
Gly	His	Tyr	Pro	Met	Ser	Gly	Gly	Pro	Ala	Met	Leu	Thr	Ser	Gln
1370						1375					1380			
Val	Cys	Glu	Asn	His	Asp	Asn	His	Tyr	Ser	Glu	Ser	Thr	Glu	Leu
1385						1390					1395			
Ser	Pro	Glu	Leu	Phe	Glu	Ser	Pro	Asn	Ile	Gln	Phe	Phe	Val	Leu
1400						1405					1410			
Asn	Asn	Thr	Thr	Leu	Val	Ser	Cys	Ile	Gln	Ile	Arg	Ser	Glu	Glu
1415						1420					1425			
Asn	Met	Pro	Gly	Gly	Gly	Leu	Ser	Ala	Gly	Leu	Ala	Ser	Ala	Asn
1430						1435					1440			
Ser	Asn	Val	Arg	Ile	Ile	Val	Arg	Asp	Leu	Ser	Gly	Lys	Tyr	Ser
1445						1450					1455			

544

Trp	Asp	Ser	Ala	Ile	Leu	Tyr	Gly	Pro	Pro	Pro	Val	Ser	Gly	Leu
1460						1465					1470			
Ser	Glu	Pro	Thr	Ser	Phe	Met	Leu	Ser	Leu	Ser	His	Gln	Glu	Lys
1475						1480					1485			
Pro	Glu	Glu	Pro	Pro	Thr	Ser	Asn	Glu	Cys	Leu	Glu	Asp	Ile	Thr
1490						1495					1500			
Val	Lys	Asp	Gly	Leu	Ser	Leu	Gln	Phe	Lys	Arg	Phe	Arg	Glu	Thr
1505						1510					1515			
Val	Pro	Thr	Trp	Asp	Thr	Ile	Arg	Asp	Glu	Glu	Asp	Val	Leu	Asp
1520						1525					1530			
Glu	Leu	Leu	Gln	Tyr	Leu	Gly	Val	Thr	Ser	Pro	Glu	Cys	Leu	Gln
1535						1540					1545			
Arg	Thr	Gly	Ile	Ser	Leu	Asn	Ile	Pro	Ala	Pro	Gln	Pro	Val	Cys
1550						1555					1560			
Ile	Ser	Glu	Lys	Gln	Glu	Asn	Asp	Val	Ile	Asn	Ala	Ile	Leu	Lys
1565						1570					1575			
Gln	His	Thr	Glu	Glu	Lys	Glu	Phe	Val	Glu	Lys	His	Phe	Asn	Asp
1580						1585					1590			
Leu	Asn	Met	Lys	Ala	Val	Glu	Gln	Asp	Glu	Pro	Ile	Pro	Gln	Lys
1595						1600					1605			
Pro	Gln	Ser	Ala	Phe	Tyr	Tyr	Cys	Arg	Leu	Leu	Leu	Ser	Ile	Leu
1610						1615					1620			
Gly	Met	Asn	Ser	Trp	Asp	Lys	Arg	Arg	Ser	Phe	His	Leu	Leu	Lys
1625						1630					1635			
Lys	Asn	Glu	Lys	Leu	Leu	Arg	Glu	Leu	Arg	Asn	Leu	Asp	Ser	Arg
1640						1645					1650			
Gln	Cys	Arg	Glu	Thr	His	Lys	Ile	Ala	Val	Phe	Tyr	Val	Ala	Glu
1655						1660					1665			
Gly	Gln	Glu	Asp	Lys	His	Ser	Ile	Leu	Thr	Asn	Thr	Gly	Gly	Ser
1670						1675					1680			
Gln	Ala	Tyr	Glu	Asp	Phe	Val	Ala	Gly	Leu	Gly	Trp	Glu	Leu	Ile

545

1685

1690

1695

Ile Phe Lys Leu Tyr Glu  
1700

&lt;210&gt; 452

&lt;211&gt; 1239

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 452

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
180 185 190



546

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

547

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp

548

675

680

685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 755 760 765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 820 825 830

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
 835 840 845

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
 850 855 860

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
 865 870 875 880

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
 885 890 895

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
 900 905 910

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
 915 920 925

549

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
 930 935 940

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
 945 950 955 960

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
 965 970 975

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
 980 985 990

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
 995 1000 1005

Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe  
 1010 1015 1020

Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile  
 1025 1030 1035

Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu  
 1040 1045 1050

Gly Leu Pro Gly Ala Thr Met Leu Ile Met Asp Phe Ile Val Ala  
 1055 1060 1065

Ala Gly Arg Val Ala Ser Ser Ala Phe Leu Asn Ala Pro Arg Val  
 1070 1075 1080

Glu Ala Gln Val Leu Leu Gly Ser Leu Val Cys Phe Pro Asn Leu  
 1085 1090 1095

Tyr Cys Glu Leu Pro Ser Leu His Pro Asn Ile Pro Asp Val Ala  
 1100 1105 1110

Val Ser Gln Phe Thr Asp Val Lys Glu Leu Ile Ile Lys Thr Val  
 1115 1120 1125

Leu Ser Ser Ala Arg Asp Glu Pro Ser Gly Pro Ala Arg Cys Val  
 1130 1135 1140

Ala Leu Cys Ser Leu Gly Ile Trp Ile Cys Glu Glu Leu Val His  
 1145 1150 1155

550

Glu Ser His His Pro Gln Ile Lys Glu Ala Leu Asn Val Ile Cys  
 1160 1165 1170

Val Ser Leu Lys Phe Thr Asn Lys Thr Val Ala His Val Ala Cys  
 1175 1180 1185

Asn Met Leu His Met Leu Val His Tyr Val Pro Arg Leu Gln Ile  
 1190 1195 1200

Tyr Gln Pro Asp Ser Pro Leu Lys Ile Ile Gln Ile Leu Ile Ala  
 1205 1210 1215

Thr Ile Thr His Leu Leu Pro Ser Thr Glu Ala Ser Ser Tyr Glu  
 1220 1225 1230

Met Asp Lys Arg Val Ile  
 1235

<210> 453  
 <211> 849  
 <212> PRT  
 <213> Homo sapien

<400> , 453

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His

551

115

120

125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

552

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

553

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 675 680 685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 755 760 765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 820 825 830

Thr Ile Thr Gly Lys Val Ile His Gly Asn Val Phe Leu Lys Cys Ile  
 835 840 845



554

Phe

<210> 454  
 <211> 284  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 454

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

555

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Val Thr Tyr Leu  
 260 265 270

Ser Val Phe Leu Ile Tyr Lys Glu Gly Phe Tyr Leu  
 275 280

<210> 455  
 <211> 607  
 <212> PRT  
 <213> Homo sapien

<400> 455

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

556

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile

557

370

375

380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Gly  
 595 600 605

&lt;210&gt; 456

&lt;211&gt; 1934

558

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 456

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

559

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile

560

465		470		475		480
Lys Ala Asn Leu	Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu					
	485		490			495
Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu						
	500		505			510
Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu						
	515		520			525
Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln						
	530		535			540
Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys						
	545		550		555	560
Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro						
	565		570			575
Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro						
	580		585			590
Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Ala Met						
	595		600			605
Arg Ser Arg Ser Ile Gly Glu Cys Ala Leu Pro Ser Ala Tyr Ile Arg						
	610		615			620
Ser Ala Lys Ser Ala Pro Val Leu Ile His Thr Ser Lys Pro Phe Leu						
	625		630		635	640
Pro Asp Ile Val Leu Thr Pro Leu Ser Asp Glu Leu Ser Asp Ile Asp						
	645		650			655
Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser Gln						
	660		665			670
Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu Gln						
	675		680			685
Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe Thr						
	690		695			700
Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu Pro						
	705		710		715	720

561

Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp Leu  
725 730 735

Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser Thr  
740 745 750

Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys Asp  
755 760 765

Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp Asp  
770 775 780

Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser Ser  
785 790 795 800

Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe Gln  
805 810 815

Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr Gly  
820 825 830

Val	Thr	Ser	Ser	Ala	Asp	Val	Asp	Ser	Gly	Ser	Gly	His	His	Gln	Ser
		835					840					845			

Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp Ser  
850 855 860

Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala Thr  
865 870 875 880

Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly Ser  
885 890 895

Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met Glu  
900 905 910

Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu Gln  
915 920 925

Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys Ser  
930 935 940

Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala Thr  
945 950 955 960



562

Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser Ile  
 - 965 970 975

Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu Leu  
 980 985 990

Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr Asp  
 995 1000 1005

Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
 1010 1015 1020

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys  
 1025 1030 1035

Tyr Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr  
 1040 1045 1050

Met Lys Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr  
 1055 1060 1065

His Phe Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln  
 1070 1075 1080

Asp Ile Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe  
 1085 1090 1095

Ser Leu Gly Leu Pro Gly Ala Thr Met Leu Ile Met Asp Phe Ile  
 1100 1105 1110

Val Ala Ala Gly Arg Val Ala Ser Ser Ala Phe Leu Asn Ala Pro  
 1115 1120 1125

Arg Val Glu Ala Gln Val Leu Leu Gly Ser Leu Val Cys Phe Pro  
 1130 1135 1140

Asn Leu Tyr Cys Glu Leu Pro Ser Leu His Pro Asn Ile Pro Asp  
 1145 1150 1155

Val Ala Val Ser Gln Phe Thr Asp Val Lys Glu Leu Ile Ile Lys  
 1160 1165 1170

Thr Val Leu Ser Ser Ala Arg Asp Glu Pro Ser Gly Pro Ala Arg  
 1175 1180 1185

563

Cys Val	Ala Leu Cys Ser	Leu	Gly Ile Trp Ile	Cys	Glu Glu Leu
1190		1195		1200	
Val His	Glu Ser His His	Pro	Gln Ile Lys Glu	Ala	Leu Asn Val
1205		1210		1215	
Ile Cys	Val Ser Leu Lys	Phe	Thr Asn Lys Thr	Val	Ala His Val
1220		1225		1230	
Ala Cys	Asn Met Leu His	Met	Leu Val His Tyr	Val	Pro Arg Leu
1235		1240		1245	
Gln Ile	Tyr Gln Pro Asp	Ser	Pro Leu Lys Ile	Ile	Gln Ile Leu
1250		1255		1260	
Ile Ala	Thr Ile Thr His	Leu	Leu Pro Ser Thr	Glu	Ala Ser Ser
1265		1270		1275	
Tyr Glu	Met Asp Lys Arg	Leu	Val Val Ser Leu	Leu	Leu Cys Leu
1280		1285		1290	
Leu Asp	Trp Ile Met Ala	Leu	Pro Leu Lys Thr	Leu	Leu Gln Pro
1295		1300		1305	
Phe His	Ala Thr Gly Ala	Glu	Ser Asp Lys Thr	Glu	Lys Ser Val
1310		1315		1320	
Leu Asn	Cys Ile Tyr Lys	Val	Leu His Gly Cys	Val	Tyr Gly Ala
1325		1330		1335	
Gln Cys	Phe Ser Asn Pro	Arg	Tyr Phe Pro Met	Ser	Leu Ser Asp
1340		1345		1350	
Leu Ala	Ser Val Asp Tyr	Asp	Pro Phe Met His	Leu	Glu Ser Leu
1355		1360		1365	
Lys Glu	Pro Glu Pro Leu	His	Ser Pro Asp Ser	Glu	Arg Ser Ser
1370		1375		1380	
Lys Leu	Gln Pro Val Thr	Glu	Val Lys Thr Gln	Met	Gln His Gly
1385		1390		1395	
Leu Ile	Ser Ile Ala Ala	Arg	Thr Val Ile Thr	His	Leu Val Asn
1400		1405		1410	
His Leu	Gly His Tyr Pro	Met	Ser Gly Gly Pro	Ala	Met Leu Thr

564

1415		1420		1425
Ser Gln Val Cys Glu Asn His Asp Asn His Tyr Ser Glu Ser Thr				
1430		1435		1440
Glu Leu Ser Pro Glu Leu Phe Glu Ser Pro Asn Ile Gln Phe Phe				
1445		1450		1455
Val Leu Asn Asn Thr Thr Leu Val Ser Cys Ile Gln Ile Arg Ser				
1460		1465		1470
Glu Glu Asn Met Pro Gly Gly Gly Leu Ser Ala Gly Leu Ala Ser				
1475		1480		1485
Ala Asn Ser Asn Val Arg Ile Ile Val Arg Asp Leu Ser Gly Lys				
1490		1495		1500
Tyr Ser Trp Asp Ser Ala Ile Leu Tyr Gly Pro Pro Pro Val Ser				
1505		1510		1515
Gly Leu Ser Glu Pro Thr Ser Phe Met Leu Ser Leu Ser His Gln				
1520		1525		1530
Glu Lys Pro Glu Glu Pro Pro Thr Ser Asn Glu Cys Leu Glu Asp				
1535		1540		1545
Ile Thr Val Lys Asp Gly Leu Ser Leu Gln Phe Lys Arg Phe Arg				
1550		1555		1560
Glu Thr Val Pro Thr Trp Asp Thr Ile Arg Asp Glu Glu Asp Val				
1565		1570		1575
Leu Asp Glu Leu Leu Gln Tyr Leu Gly Val Thr Ser Pro Glu Cys				
1580		1585		1590
Leu Gln Arg Thr Gly Ile Ser Leu Asn Ile Pro Ala Pro Gln Pro				
1595		1600		1605
Val Cys Ile Ser Glu Lys Gln Glu Asn Asp Val Ile Asn Ala Ile				
1610		1615		1620
Leu Lys Gln His Thr Glu Glu Lys Glu Phe Val Glu Lys His Phe				
1625		1630		1635
Asn Asp Leu Asn Met Lys Ala Val Glu Gln Asp Glu Pro Ile Pro				
1640		1645		1650

565

Gln Lys	Pro Gln Ser Ala Phe	Tyr Tyr Cys Arg	Leu	Leu Leu Ser
1655		1660	1665	
Ile Leu	Gly Met Asn Ser Trp	Asp Lys Arg Arg	Ser	Phe His Leu
1670		1675	1680	
Leu Lys	Lys Asn Glu Lys	Leu	Leu Arg Glu Leu Arg	Asn Leu Asp
1685		1690	1695	
Ser Arg	Gln Cys Arg Glu Thr	His Lys Ile Ala	Val	Phe Tyr Val
1700		1705	1710	
Ala Glu	Gly Gln Glu Asp	Lys	His Ser Ile Leu Thr	Asn Thr Gly
1715		1720	1725	
Gly Ser	Gln Ala Tyr Glu	Asp	Phe Val Ala Gly	Leu Gly Trp Glu
1730		1735	1740	
Val Asn	Leu Thr Asn His	Cys	Gly Phe Met Gly	Gly Leu Gln Lys
1745		1750	1755	
Asn Lys	Ser Thr Gly Leu	Thr	Thr Pro Tyr Phe	Ala Thr Ser Thr
1760		1765	1770	
Val Glu	Val Ile Phe His	Val	Ser Thr Arg Met	Pro Ser Asp Ser
1775		1780	1785	
Asp Asp	Ser Leu Thr Lys	Lys	Leu Arg His Leu	Gly Asn Asp Glu
1790		1795	1800	
Val His	Ile Val Trp Ser	Glu	His Thr Arg Asp	Tyr Arg Arg Gly
1805		1810	1815	
Ile Ile	Pro Thr Glu Phe	Gly	Asp Val Leu Ile	Val Ile Tyr Pro
1820		1825	1830	
Met Lys	Asn His Met Phe	Ser	Ile Gln Ile Met	Lys Lys Pro Glu
1835		1840	1845	
Val Pro	Phe Phe Gly Pro	Leu	Phe Asp Gly Ala	Ile Val Asn Gly
1850		1855	1860	
Lys Val	Leu Pro Ile Met	Val	Arg Ala Thr Ala	Ile Asn Ala Ser
1865		1870	1875	

566

Arg Ala Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Phe Tyr Glu  
 1880 1885 1890

Glu Arg Ala Arg Tyr Leu Gln Thr Ile Val Gln His His Leu Glu  
 1895 1900 1905

Pro Thr Thr Phe Glu Asp Phe Ala Ala Gln Val Phe Ser Pro Ala  
 1910 1915 1920

Pro Tyr His His Leu Pro Ser Asp Ala Asp His  
 1925 1930

<210> 457

<211> 1220

<212> PRT

<213> Homo sapien

<400> 457

Met Ser Gln Lys Leu Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser  
 1 5 10 15

Ala Asn Val Pro Asp Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg  
 20 25 30

Ser Gly Asn Ala Ser Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser  
 35 40 45

Leu Glu Ile Pro Lys Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln  
 50 55 60

Met Arg Pro Ile Asp Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro  
 65 70 75 80

Ala Ser Ala Gly Ser Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp  
 85 90 95

Ser Phe Ser Ala Phe Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly  
 100 105 110

Phe Gly Thr Asp Thr Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly  
 115 120 125

Ser Gly His His Gln Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr  
 130 135 140

Thr Leu His Ile Asp Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe

567

145		150		155		160
Ser Ala Glu Val	Ala Thr Ile Thr Gly	Ser Glu Ser Ala	Ser Pro Val			
	165	170	175			
His Ser Pro Leu	Gly Ser Arg Ser Gln Thr	Pro Ser Pro	Ser Thr Leu			
	180	185	190			
Asn Ile Asp His	Met Glu Gln Lys Asp Leu	Gln Leu Asp	Glu Lys Leu			
	195	200	205			
His His Ser Val	Leu Gln Thr Pro Asp Asp	Leu Glu Ile	Ser Glu Phe			
	210	215	220			
Pro Ser Glu Cys	Cys Ser Val Met Ala Gly	Gly Thr Leu Thr	Gly Trp			
225	230	235	240			
His Ala Asp Val	Ala Thr Val Met Trp Arg	Arg Met Leu	Gly Ile Leu			
	245	250	255			
Gly Asp Val Asn	Ser Ile Met Asp Pro Glu	Ile His Ala	Gln Val Phe			
	260	265	270			
Asp Tyr Leu Cys	Glu Leu Trp Gln Asn Leu	Ala Lys Ile	Arg Asp Asn			
	275	280	285			
Leu Gly Ile Ser	Thr Asp Asn Leu Thr Ser	Pro Ser Pro	Pro Val Leu			
	290	295	300			
Ile Pro Pro Leu	Arg Ile Leu Thr Pro Trp	Leu Phe Lys	Ala Thr Met			
305	310	315	320			
Leu Thr Asp Lys	Tyr Lys Gln Gly Lys Leu	His Ala Tyr	Lys Leu Ile			
	325	330	335			
Cys Asn Thr Met	Lys Arg Arg Gln Asp Val	Ser Pro Asn	Arg Asp Phe			
	340	345	350			
Leu Thr His Phe	Tyr Asn Ile Met His Cys	Gly Leu Leu	His Ile Asp			
	355	360	365			
Gln Asp Ile Val	Asn Thr Ile Ile Lys His	Cys Ser Pro	Gln Phe Phe			
	370	375	380			
Ser Leu Gly Leu	Pro Gly Ala Thr Met Leu	Ile Met Asp	Phe Ile Val			
385	390	395	400			

568

Ala Ala Gly Arg Val Ala Ser Ser Ala Phe Leu Asn Ala Pro Arg Val  
 405 410 415

Glu Ala Gln Val Leu Leu Gly Ser Leu Val Cys Phe Pro Asn Leu Tyr  
 420 425 430

Cys Glu Leu Pro Ser Leu His Pro Asn Ile Pro Asp Val Ala Val Ser  
 435 440 445

Gln Phe Thr Asp Val Lys Glu Leu Ile Ile Lys Thr Val Leu Ser Ser  
 450 455 460

Ala Arg Asp Glu Pro Ser Gly Pro Ala Arg Cys Val Ala Leu Cys Ser  
 465 470 475 480

Leu Gly Ile Trp Ile Cys Glu Glu Leu Val His Glu Ser His His Pro  
 485 490 495

Gln Ile Lys Glu Ala Leu Asn Val Ile Cys Val Ser Leu Lys Phe Thr  
 500 505 510

Asn Lys Thr Val Ala His Val Ala Cys Asn Met Leu His Met Leu Val  
 515 520 525

His Tyr Val Pro Arg Leu Gln Ile Tyr Gln Pro Asp Ser Pro Leu Lys  
 530 535 540

Ile Ile Gln Ile Leu Ile Ala Thr Ile Thr His Leu Leu Pro Ser Thr  
 545 550 555 560

Glu Ala Ser Ser Tyr Glu Met Asp Lys Arg Leu Val Val Ser Leu Leu  
 565 570 575

Leu Cys Leu Leu Asp Trp Ile Met Ala Leu Pro Leu Lys Thr Leu Leu  
 580 585 590

Gln Pro Phe His Ala Thr Gly Ala Glu Ser Asp Lys Thr Glu Lys Ser  
 595 600 605

Val Leu Asn Cys Ile Tyr Lys Val Leu His Gly Cys Val Tyr Gly Ala  
 610 615 620

Gln Cys Phe Ser Asn Pro Arg Tyr Phe Pro Met Ser Leu Ser Asp Leu  
 625 630 635 640

569

Ala Ser Val Asp Tyr Asp Pro Phe Met His Leu Glu Ser Leu Lys Glu  
                     645                    650                    655

Pro Glu Pro Leu His Ser Pro Asp Ser Glu Arg Ser Ser Lys Leu Gln  
                     660                    665                    670

Pro Val Thr Glu Val Lys Thr Gln Met Gln His Gly Leu Ile Ser Ile  
                     675                    680                    685

Ala Ala Arg Thr Val Ile Thr His Leu Val Asn His Leu Gly His Tyr  
                     690                    695                    700

Pro Met Ser Gly Gly Pro Ala Met Leu Thr Ser Gln Val Cys Glu Asn  
                     705                    710                    715                    720

His Asp Asn His Tyr Ser Glu Ser Thr Glu Leu Ser Pro Glu Leu Phe  
                     725                    730                    735

Glu Ser Pro Asn Ile Gln Phe Phe Val Leu Asn Asn Thr Thr Leu Val  
                     740                    745                    750

Ser Cys Ile Gln Ile Arg Ser Glu Glu Asn Met Pro Gly Gly Gly Leu  
                     755                    760                    765

Ser Ala Gly Leu Ala Ser Ala Asn Ser Asn Val Arg Ile Ile Val Arg  
                     770                    775                    780

Asp Leu Ser Gly Lys Tyr Ser Trp Asp Ser Ala Ile Leu Tyr Gly Pro  
                     785                    790                    795                    800

Pro Pro Val Ser Gly Leu Ser Glu Pro Thr Ser Phe Met Leu Ser Leu  
                     805                    810                    815

Ser His Gln Glu Lys Pro Glu Glu Pro Pro Thr Ser Asn Glu Cys Leu  
                     820                    825                    830

Glu Asp Ile Thr Val Lys Asp Gly Leu Ser Leu Gln Phe Lys Arg Phe  
                     835                    840                    845

Arg Glu Thr Val Pro Thr Trp Asp Thr Ile Arg Asp Glu Glu Asp Val  
                     850                    855                    860

Leu Asp Glu Leu Leu Gln Tyr Leu Gly Val Thr Ser Pro Glu Cys Leu  
                     865                    870                    875                    880



570

Gln Arg Thr Gly Ile Ser Leu Asn Ile Pro Ala Pro Gln Pro Val Cys  
 885 890 895

Ile Ser Glu Lys Gln Glu Asn Asp Val Ile Asn Ala Ile Leu Lys Gln  
 900 905 910

His Thr Glu Glu Lys Glu Phe Val Glu Lys His Phe Asn Asp Leu Asn  
 915 920 925

Met Lys Ala Val Glu Gln Asp Glu Pro Ile Pro Gln Lys Pro Gln Ser  
 930 935 940

Ala Phe Tyr Tyr Cys Arg Leu Leu Leu Ser Ile Leu Gly Met Asn Ser  
 945 950 955 960

Trp Asp Lys Arg Arg Ser Phe His Leu Leu Lys Lys Asn Glu Lys Leu  
 965 970 975

Leu Arg Glu Leu Arg Asn Leu Asp Ser Arg Gln Cys Arg Glu Thr His  
 980 985 990

Lys Ile Ala Val Phe Tyr Val Ala Glu Gly Gln Glu Asp Lys His Ser  
 995 1000 1005

Ile Leu Thr Asn Thr Gly Gly Ser Gln Ala Tyr Glu Asp Phe Val  
 1010 1015 1020

Ala Gly Leu Gly Trp Glu Val Asn Leu Thr Asn His Cys Gly Phe  
 1025 1030 1035

Met Gly Gly Leu Gln Lys Asn Lys Ser Thr Gly Leu Thr Thr Pro  
 1040 1045 1050

Tyr Phe Ala Thr Ser Thr Val Glu Val Ile Phe His Val Ser Thr  
 1055 1060 1065

Arg Met Pro Ser Asp Ser Asp Asp Ser Leu Thr Lys Lys Leu Arg  
 1070 1075 1080

His Leu Gly Asn Asp Glu Val His Ile Val Trp Ser Glu His Thr  
 1085 1090 1095

Arg Asp Tyr Arg Arg Gly Ile Ile Pro Thr Glu Phe Gly Asp Val  
 1100 1105 1110

Leu Ile Val Ile Tyr Pro Met Lys Asn His Met Phe Ser Ile Gln

571

1115

1120

1125

Ile Met Lys Lys Pro Glu Val Pro Phe Phe Gly Pro Leu Phe Asp  
 1130 1135 1140

Gly Ala Ile Val Asn Gly Lys Val Leu Pro Ile Met Val Arg Ala  
 1145 1150 1155

Thr Ala Ile Asn Ala Ser Arg Ala Leu Lys Ser Leu Ile Pro Leu  
 1160 1165 1170

Tyr Gln Asn Phe Tyr Glu Glu Arg Ala Arg Tyr Leu Gln Thr Ile  
 1175 1180 1185

Val Gln His His Leu Glu Pro Thr Thr Phe Glu Asp Phe Ala Ala  
 1190 1195 1200

Gln Val Phe Ser Pro Ala Pro Tyr His His Leu Pro Ser Asp Ala  
 1205 1210 1215

Asp His  
 1220

<210> 458  
 <211> 1126  
 <212> PRT  
 <213> Homo sapien

<400> 458

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

572

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

573

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro

574

580

585

590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 675 680 685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 755 760 765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 820 825 830

575

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
 835 840 845

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
 850 855 860

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
 865 870 875 880

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
 885 890 895

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
 900 905 910

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
 915 920 925

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
 930 935 940

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
 945 950 955 960

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
 965 970 975

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
 980 985 990

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
 995 1000 1005

Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe  
 1010 1015 1020

Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile  
 1025 1030 1035

Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu  
 1040 1045 1050

Gly Leu Pro Gly Ala Thr Met Leu Ile Met Asp Phe Ile Val Ala  
 1055 1060 1065

576

Ala Gly Arg Val Ala Ser Ser Ala Phe Leu Asn Ala Pro Arg Val  
 1070 1075 1080

Glu Ala Gln Val Leu Leu Gly Ser Leu Val Cys Phe Pro Asn Leu  
 1085 1090 1095

Tyr Cys Glu Leu Pro Ser Leu His Pro Asn Ile Pro Asp Val Ala  
 1100 1105 1110

Val Ser Gln Phe Thr Asp Val Lys Met Cys Ser Thr Leu  
 1115 1120 1125

<210> 459

<211> 1894

<212> PRT

<213> Homo sapien

<400> 459

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu

577

145		150		155		160
Val Ser Phe Trp	Leu Glu Pro Lys	Pro His Thr	Gly Pro His	Ile Pro		
	165		170		175	
Gly Met Glu Gly	Glu Val Leu Pro	Lys Asn Ile	Gln Arg Ala	Ala Ala Ala		
	180		185		190	
Ser Leu Val Ser	Arg Glu Glu Ser	Lys Asn Asp	Asn Ala Asp	Lys Thr		
	195		200		205	
Asp Arg Thr Thr	Glu Pro Glu Gln	Ser His Ser	Asn Thr Ser	Thr Leu		
	210		215		220	
Thr Glu Arg Glu	Pro Ser Ser Ser	Ser Leu Cys	Ser Ile Asp	Glu Glu		
	225		230		235	240
His Leu Thr Asp	Ile Glu Ile Val	Arg Arg Val	Phe Ser Ser	Lys Arg		
	245		250		255	
Ser Asn Val Asn	Phe Val Thr Glu	Ile Phe Arg	Gln Ala Phe	Leu Leu		
	260		265		270	
Pro Ile Cys Glu	Ala Ala Ala Met	Arg Lys Val	Val Lys Val	Tyr Gln		
	275		280		285	
Glu Trp Ile Gln	Gln Glu Glu Lys	Pro Leu Phe	Met Gln Glu	Pro Glu		
	290		295		300	
Glu Ile Val Ile	Thr Ser Ser Asp	Leu Pro Cys	Ile Glu Asn	Val Thr		
	305		310		315	320
Asp His Asp Ile	Ser Met Glu Glu	Gly Glu Lys	Arg Glu Glu	Glu Asn		
	325		330		335	
Gly Thr Asn Thr	Ala Asp His Val	Arg Asn Ser	Ser Trp Ala	Lys Asn		
	340		345		350	
Gly Ser Tyr Gln	Gly Ala Leu His	Asn Ala Ser	Glu Glu Ala	Thr Glu		
	355		360		365	
Gln Asn Ile Arg	Ala Gly Thr Gln	Ala Val Leu	Gln Val Phe	Ile Ile		
	370		375		380	
Asn Ser Ser Asn	Ile Phe Leu Leu	Glu Pro Ala	Asn Glu Ile	Lys Asn		
	385		390		395	400



578

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln	Pro	Leu	Pro	Arg	Ser	Ser	Ser	Thr	Ser	Asp	Ile	Leu	Glu	Pro	Phe	
				645					650					655		
Thr	Val	Glu	Arg	Ala	Lys	Val	Asn	Lys	Glu	Asp	Met	Ser	Gln	Lys	Leu	
				660					665					670		
Pro	Pro	Leu	Asn	Ser	Asp	Ile	Gly	Gly	Ser	Ser	Ala	Asn	Val	Pro	Asp	
				675					680					685		
Leu	Met	Asp	Glu	Phe	Ile	Ala	Glu	Arg	Leu	Arg	Ser	Gly	Asn	Ala	Ser	
				690					695					700		
Thr	Met	Thr	Arg	Arg	Gly	Ser	Ser	Pro	Gly	Ser	Leu	Glu	Ile	Pro	Lys	
				705					710					715		
Asp	Leu	Pro	Asp	Ile	Leu	Asn	Lys	Gln	Asn	Gln	Met	Arg	Pro	Ile	Asp	
				725					730					735		
Asp	Pro	Gly	Val	Pro	Ser	Glu	Trp	Thr	Ser	Pro	Ala	Ser	Ala	Gly	Ser	
				740					745					750		
Ser	Asp	Leu	Ile	Ser	Ser	Asp	Ser	His	Ser	Asp	Ser	Phe	Ser	Ala	Phe	
				755					760					765		
Gln	Tyr	Asp	Gly	Arg	Lys	Phe	Asp	Asn	Phe	Gly	Phe	Gly	Thr	Asp	Thr	
				770					775					780		
Gly	Val	Thr	Ser	Ser	Ala	Asp	Val	Asp	Ser	Gly	Ser	Gly	His	His	Gln	
				785					790					795		
Ser	Ala	Glu	Glu	Gln	Glu	Val	Ala	Ser	Leu	Thr	Thr	Leu	His	Ile	Asp	
				805					810					815		
Ser	Glu	Thr	Ser	Ser	Leu	Asn	Gln	Gln	Ala	Phe	Ser	Ala	Glu	Val	Ala	
				820					825					830		
Thr	Ile	Thr	Gly	Ser	Glu	Ser	Ala	Ser	Pro	Val	His	Ser	Pro	Leu	Gly	
				835					840					845		
Ser	Arg	Ser	Gln	Thr	Pro	Ser	Pro	Ser	Thr	Leu	Asn	Ile	Asp	His	Met	
				850					855					860		
Glu	Gln	Lys	Asp	Leu	Gln	Leu	Asp	Glu	Lys	Leu	His	His	Ser	Val	Leu	
				865					870					875		

Gln	Thr	Pro	Asp	Asp	Leu	Glu	Ile	Ser	Glu	Phe	Pro	Ser	Glu	Cys	Cys
				885					890						
				885					890						
Ser	Val	Met	Ala	Gly	Gly	Thr	Leu	Thr	Gly	Trp	His	Ala	Asp	Val	Ala
				900					905						
				900					905						
Thr	Val	Met	Trp	Arg	Arg	Met	Leu	Gly	Ile	Leu	Gly	Asp	Val	Asn	Ser
				915					920						
				915					920						
Ile	Met	Asp	Pro	Glu	Ile	His	Ala	Gln	Val	Phe	Asp	Tyr	Leu	Cys	Glu
				930					935						
				930					935						
Leu	Trp	Gln	Asn	Leu	Ala	Lys	Ile	Arg	Asp	Asn	Leu	Gly	Ile	Ser	Thr
				945					950						
				945					950						
Asp	Asn	Leu	Thr	Ser	Pro	Ser	Pro	Pro	Val	Leu	Ile	Pro	Pro	Leu	Arg
				965					970						
				965					970						
Ile	Leu	Thr	Pro	Trp	Leu	Phe	Lys	Ala	Thr	Met	Leu	Thr	Asp	Lys	Tyr
				980					985						
				980					985						
Lys	Gln	Gly	Lys	Leu	His	Ala	Tyr	Lys	Leu	Ile	Cys	Asn	Thr	Met	L
				995					1000						
				995					1000						
Arg	Arg	Gln	Asp	Val	Ser	Pro	Asn	Arg	Asp	Phe	Leu	Thr	His	Phe	
				1010					1015						
				1010					1015						
Tyr	Asn	Ile	Met	His	Cys	Gly	Leu	Leu	His	Ile	Asp	Gln	Asp	Ile	
				1025					1030						
				1025					1030						
Val	Asn	Thr	Ile	Ile	Lys	His	Cys	Ser	Pro	Gln	Phe	Phe	Ser	Leu	
				1040					1045						
				1040					1045						
Gly	Leu	Pro	Gly	Ala	Thr	Met	Leu	Ile	Met	Asp	Phe	Ile	Val	Ala	
				1055					1060						
				1055					1060						
Ala	Gly	Arg	Val	Ala	Ser	Ser	Ala	Phe	Leu	Asn	Ala	Pro	Arg	Val	
				1070					1075						
				1070					1075						
Glu	Ala	Gln	Val	Leu	Leu	Gly	Ser	Leu	Val	Cys	Phe	Pro	Asn	Leu	
				1085					1090						
				1085					1090						
Tyr	Cys	Glu	Leu	Pro	Ser	Leu	His	Pro	Asn	Ile	Pro	Asp	Val	Ala	
				1100					1105						
				1100					1105						
Val	Ser	Gln	Phe	Thr	Asp	Val	Lys	Glu	Leu	Ile	Ile	Lys	Thr	Val	

581

1115		1120		1125
Leu Ser	Ser Ala Arg Asp	Glu Pro Ser Gly	Pro Ala	Arg Cys Val
1130		1135		1140
Ala Leu	Cys Ser Leu Gly	Ile Trp Ile Cys	Glu Glu	Leu Val His
1145		1150		1155
Glu Ser	His His Pro Gln	Ile Lys Glu Ala	Leu Asn	Val Ile Cys
1160		1165		1170
Val Ser	Leu Lys Phe Thr	Asn Lys Thr Val	Ala His	Val Ala Cys
1175		1180		1185
Asn Met	Leu His Met Leu	Val His Tyr Val	Pro Arg	Leu Gln Ile
1190		1195		1200
Tyr Gln	Pro Asp Ser Pro	Leu Lys Ile Ile	Gln Ile	Leu Ile Ala
1205		1210		1215
Thr Ile	Thr His Leu Leu	Pro Ser Thr Glu	Ala Ser	Ser Tyr Glu
1220		1225		1230
Met Asp	Lys Arg Leu Val	Val Ser Leu Leu	Leu Cys	Leu Leu Asp
1235		1240		1245
Trp Ile	Met Ala Leu Pro	Leu Lys Thr Leu	Leu Gln	Pro Phe His
1250		1255		1260
Ala Thr	Gly Ala Glu Ser	Asp Lys Thr Glu	Lys Ser	Val Leu Asn
1265		1270		1275
Cys Ile	Tyr Lys Val Leu	His Gly Cys Val	Tyr Gly	Ala Gln Cys
1280		1285		1290
Phe Ser	Asn Pro Arg Tyr	Phe Pro Met Ser	Leu Ser	Asp Leu Ala
1295		1300		1305
Ser Val	Asp Tyr Asp Pro	Phe Met His Leu	Glu Ser	Leu Lys Glu
1310		1315		1320
Pro Glu	Pro Leu His Ser	Pro Asp Ser Glu	Arg Ser	Ser Lys Leu
1325		1330		1335
Gln Pro	Val Thr Glu Val	Lys Thr Gln Met	Gln His	Gly Leu Ile
1340		1345		1350



583

Gln His Thr Glu Glu Lys Glu Phe Val Glu Lys His Phe Asn Asp	
1580	1585 1590
Leu Asn Met Lys Ala Val Glu Gln Asp Glu Pro Ile Pro Gln Lys	
1595	1600 1605
Pro Gln Ser Ala Phe Tyr Tyr Cys Arg Leu Leu Leu Ser Ile Leu	
1610	1615 1620
Gly Met Asn Ser Trp Asp Lys Arg Arg Ser Phe His Leu Leu Lys	
1625	1630 1635
Lys Asn Glu Lys Leu Leu Arg Glu Leu Arg Asn Leu Asp Ser Arg	
1640	1645 1650
Gln Cys Arg Glu Thr His Lys Ile Ala Val Phe Tyr Val Ala Glu	
1655	1660 1665
Gly Gln Glu Asp Lys His Ser Ile Leu Thr Asn Thr Gly Gly Ser	
1670	1675 1680
Gln Ala Tyr Glu Asp Phe Val Ala Gly Leu Gly Trp Glu Val Asn	
1685	1690 1695
Leu Thr Asn His Cys Gly Phe Met Gly Gly Leu Gln Lys Asn Lys	
1700	1705 1710
Ser Thr Gly Leu Thr Thr Pro Tyr Phe Ala Thr Ser Thr Val Glu	
1715	1720 1725
Val Ile Phe His Val Ser Thr Arg Met Pro Ser Asp Ser Asp Asp	
1730	1735 1740
Ser Leu Thr Lys Lys Leu Arg His Leu Gly Asn Asp Glu Val His	
1745	1750 1755
Ile Val Trp Ser Glu His Thr Arg Asp Tyr Arg Arg Gly Ile Ile	
1760	1765 1770
Pro Thr Glu Phe Gly Asp Val Leu Ile Val Ile Tyr Pro Met Lys	
1775	1780 1785
Asn His Met Phe Ser Ile Gln Ile Met Lys Lys Pro Glu Val Pro	
1790	1795 1800

584

Phe Phe Gly Pro Leu Phe Asp Gly Ala Ile Val Asn Gly Lys Val  
 1805 1810 1815

Leu Pro Ile Met Val Arg Ala Thr Ala Ile Asn Ala Ser Arg Ala  
 1820 1825 1830

Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Phe Tyr Glu Glu Arg  
 1835 1840 1845

Ala Arg Tyr Leu Gln Thr Ile Val Gln His His Leu Glu Pro Thr  
 1850 1855 1860

Thr Phe Glu Asp Phe Ala Ala Gln Val Phe Ser Pro Ala Pro Tyr  
 1865 1870 1875

His His Leu Pro Ser Asp Ala Gly Leu Leu Pro Arg Asp Ser Thr  
 1880 1885 1890

Gln

<210> 460  
 <211> 1867  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 460

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

585

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350



586

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

587

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 675 680 685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 755 760 765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 820 825 830

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly

588

835	840	845
Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met		
850	855	860
Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu		
865	870	875 880
Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys		
	885	890 895
Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala		
	900	905 910
Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser		
	915	920 925
Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu		
	930	935 940
Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr		
945	950	955 960
Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg		
	965	970 975
Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr		
	980	985 990
Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys		
	995	1000 1005
Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe		
1010	1015	1020
Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile		
1025	1030	1035
Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu		
1040	1045	1050
Gly Leu Pro Gly Ala Thr Met Leu Ile Met Asp Phe Ile Val Ala		
1055	1060	1065
Ala Gly Arg Val Ala Ser Ser Ala Phe Leu Asn Ala Pro Arg Val		
1070	1075	1080

589

Glu	Ala	Gln	Val	Leu	Leu	Gly	Ser	Leu	Val	Cys	Phe	Pro	Asn	Leu
1085						1090					1095			
Tyr	Cys	Glu	Leu	Pro	Ser	Leu	His	Pro	Asn	Ile	Pro	Asp	Val	Ala
1100						1105					1110			
Val	Ser	Gln	Phe	Thr	Asp	Val	Lys	Glu	Leu	Ile	Ile	Lys	Thr	Val
1115						1120					1125			
Leu	Ser	Ser	Ala	Arg	Asp	Glu	Pro	Ser	Gly	Pro	Ala	Arg	Cys	Val
1130						1135					1140			
Ala	Leu	Cys	Ser	Leu	Gly	Ile	Trp	Ile	Cys	Glu	Glu	Leu	Val	His
1145						1150					1155			
Glu	Ser	His	His	Pro	Gln	Ile	Lys	Glu	Ala	Leu	Asn	Val	Ile	Cys
1160						1165					1170			
Val	Ser	Leu	Lys	Phe	Thr	Asn	Lys	Thr	Val	Ala	His	Val	Ala	Cys
1175						1180					1185			
Asn	Met	Leu	His	Met	Leu	Val	His	Tyr	Val	Pro	Arg	Leu	Gln	Ile
1190						1195					1200			
Tyr	Gln	Pro	Asp	Ser	Pro	Leu	Lys	Ile	Ile	Gln	Ile	Leu	Ile	Ala
1205						1210					1215			
Thr	Ile	Thr	His	Leu	Leu	Pro	Ser	Thr	Glu	Ala	Ser	Ser	Tyr	Glu
1220						1225					1230			
Met	Asp	Lys	Arg	Leu	Val	Val	Ser	Leu	Leu	Leu	Cys	Leu	Leu	Asp
1235						1240					1245			
Trp	Ile	Met	Ala	Leu	Pro	Leu	Lys	Thr	Leu	Leu	Gln	Pro	Phe	His
1250						1255					1260			
Ala	Thr	Gly	Ala	Glu	Ser	Asp	Lys	Thr	Glu	Lys	Ser	Val	Leu	Asn
1265						1270					1275			
Cys	Ile	Tyr	Lys	Val	Leu	His	Gly	Cys	Val	Tyr	Gly	Ala	Gln	Cys
1280						1285					1290			
Phe	Ser	Asn	Pro	Arg	Tyr	Phe	Pro	Met	Ser	Leu	Ser	Asp	Leu	Ala
1295						1300					1305			

590

Ser Val	Asp Tyr	Asp Pro	Phe Met	His Leu	Glu Ser	Leu Lys	Glu
1310			1315		1320		
Pro Glu	Pro Leu	His Ser	Pro Asp	Ser Glu	Arg Ser	Ser Lys	Leu
1325			1330		1335		
Gln Pro	Val Thr	Glu Val	Lys Thr	Gln Met	Gln His	Gly Leu	Ile
1340			1345		1350		
Ser Ile	Ala Ala	Arg Thr	Val Ile	Thr His	Leu Val	Asn His	Leu
1355			1360		1365		
Gly His	Tyr Pro	Met Ser	Gly Gly	Pro Ala	Met Leu	Thr Ser	Gln
1370			1375		1380		
Val Cys	Glu Asn	His Asp	Asn His	Tyr Ser	Glu Ser	Thr Glu	Leu
1385			1390		1395		
Ser Pro	Glu Leu	Phe Glu	Ser Pro	Asn Ile	Gln Phe	Phe Val	Leu
1400			1405		1410		
Asn Asn	Thr Thr	Leu Val	Ser Cys	Ile Gln	Ile Arg	Ser Glu	Glu
1415			1420		1425		
Asn Met	Pro Gly	Gly Gly	Leu Ser	Ala Gly	Leu Ala	Ser Ala	Asn
1430			1435		1440		
Ser Asn	Val Arg	Ile Ile	Val Arg	Asp Leu	Ser Gly	Lys Tyr	Ser
1445			1450		1455		
Trp Asp	Ser Ala	Ile Leu	Tyr Gly	Pro Pro	Pro Val	Ser Gly	Leu
1460			1465		1470		
Ser Glu	Pro Thr	Ser Phe	Met Leu	Ser Leu	Ser His	Gln Glu	Lys
1475			1480		1485		
Pro Glu	Glu Pro	Pro Thr	Ser Asn	Glu Cys	Leu Glu	Asp Ile	Thr
1490			1495		1500		
Val Lys	Asp Gly	Leu Ser	Leu Gln	Phe Lys	Arg Phe	Arg Glu	Thr
1505			1510		1515		
Val Pro	Thr Trp	Asp Thr	Ile Arg	Asp Glu	Glu Asp	Val Leu	Asp
1520			1525		1530		

591

Glu Leu	Leu Gln Tyr Leu Gly	Val Thr Ser Pro Glu	Cys Leu Gln
1535	1540	1545	
Arg Thr	Gly Ile Ser Leu Asn	Ile Pro Ala Pro Gln	Pro Val Cys
1550	1555	1560	
Ile Ser	Glu Lys Gln Glu Asn	Asp Val Ile Asn Ala	Ile Leu Lys
1565	1570	1575	
Gln His	Thr Glu Glu Lys Glu	Phe Val Glu Lys His	Phe Asn Asp
1580	1585	1590	
Leu Asn	Met Lys Ala Val Glu	Cln Asp Glu Pro Ile	Pro Gln Lys
1595	1600	1605	
Pro Gln	Ser Ala Phe Tyr Tyr	Cys Arg Leu Leu Leu	Ser Ile Leu
1610	1615	1620	
Gly Met	Asn Ser Trp Asp Lys	Arg Arg Ser Phe His	Leu Leu Lys
1625	1630	1635	
Lys Asn	Glu Lys Leu Leu Arg	Glu Leu Arg Asn Leu	Asp Ser Arg
1640	1645	1650	
Gln Cys	Arg Glu Thr His Lys	Ile Ala Val Phe Tyr	Val Ala Glu
1655	1660	1665	
Gly Gln	Glu Asp Lys His Ser	Ile Leu Thr Asn Thr	Gly Gly Ser
1670	1675	1680	
Gln Ala	Tyr Glu Asp Phe Val	Ala Gly Leu Gly Trp	Glu Val Asn
1685	1690	1695	
Leu Thr	Asn His Cys Gly Phe	Met Gly Gly Leu Gln	Lys Asn Lys
1700	1705	1710	
Ser Thr	Gly Leu Thr Thr Pro	Tyr Phe Ala Thr Ser	Thr Val Glu
1715	1720	1725	
Leu Arg	His Leu Gly Asn Asp	Glu Val His Ile Val	Trp Ser Glu
1730	1735	1740	
His Thr	Arg Asp Tyr Arg Arg	Gly Ile Ile Pro Thr	Glu Phe Gly
1745	1750	1755	
Asp Val	Leu Ile Val Ile Tyr	Pro Met Lys Asn His	Met Phe Ser

592

1760	1765	1770
Ile Gln Ile Met Lys Lys Pro Glu Val Pro Phe Phe Gly Pro Leu 1775 1780 1785		
Phe Asp Gly Ala Ile Val Asn Gly Lys Val Leu Pro Ile Met Val 1790 1795 1800		
Arg Ala Thr Ala Ile Asn Ala Ser Arg Ala Leu Lys Ser Leu Ile 1805 1810 1815		
Pro Leu Tyr Gln Asn Phe Tyr Glu Glu Arg Ala Arg Tyr Leu Gln 1820 1825 1830		
Thr Ile Val Gln His His Leu Glu Pro Thr Thr Phe Glu Asp Phe 1835 1840 1845		
Ala Ala Gln Val Phe Ser Pro Ala Pro Tyr His His Leu Pro Ser 1850 1855 1860		
Asp Ala Asp His 1865		
<210> 461		
<211> 1906		
<212> PRT		
<213> Homo sapien		
<400> 461		
Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His 1 5 10 15		
Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln 20 25 30		
Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln 35 40 45		
Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala 50 55 60		
Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn 65 70 75 80		
Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys 85 90 95		

593

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335



594

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro

595

580

585

590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 675 680 685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 755 760 765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
 785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
 805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
 820 825 830

596

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
 835 840 845

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
 850 855 860

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
 865 870 875 880

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
 885 890 895

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
 900 905 910

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
 915 920 925

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
 930 935 940

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
 945 950 955 960

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
 965 970 975

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
 980 985 990

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
 995 1000 1005

Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe  
 1010 1015 1020

Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile  
 1025 1030 1035

Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu  
 1040 1045 1050

Gly Leu Pro Gly Ala Thr Met Leu Ile Met Asp Phe Ile Val Ala  
 1055 1060 1065

597

Ala Gly	Arg Val	Ala Ser	Ser	Ala Phe	Leu Asn	Ala	Pro Arg	Val
1070			1075			1080		
Glu Ala	Gln Val	Leu Leu	Gly	Ser Leu	Val Cys	Phe	Pro Asn	Leu
1085			1090			1095		
Tyr Cys	Glu Leu	Pro Ser	Leu	His Pro	Asn Ile	Pro	Asp Val	Ala
1100			1105			1110		
Val Ser	Gln Phe	Thr Asp	Val	Lys Glu	Leu Ile	Ile	Lys Thr	Val
1115			1120			1125		
Leu Ser	Ser Ala	Arg Asp	Glu	Pro Ser	Gly Pro	Ala	Arg Cys	Val
1130			1135			1140		
Ala Leu	Cys Ser	Leu Gly	Ile	Trp Ile	Cys Glu	Glu	Leu Val	His
1145			1150			1155		
Glu Ser	His His	Pro Gln	Ile	Lys Glu	Ala Leu	Asn	Val Ile	Cys
1160			1165			1170		
Val Ser	Leu Lys	Phe Thr	Asn	Lys Thr	Val Ala	His	Val Ala	Cys
1175			1180			1185		
Asn Met	Leu His	Met Leu	Val	His Tyr	Val Pro	Arg	Leu Gln	Ile
1190			1195			1200		
Tyr Gln	Pro Asp	Ser Pro	Leu	Lys Ile	Ile Gln	Ile	Leu Ile	Ala
1205			1210			1215		
Thr Ile	Thr His	Leu Leu	Pro	Ser Thr	Glu Ala	Ser	Ser Tyr	Glu
1220			1225			1230		
Met Asp	Lys Arg	Leu Val	Val	Ser Leu	Leu Leu	Cys	Leu Leu	Asp
1235			1240			1245		
Trp Ile	Met Ala	Leu Pro	Leu	Lys Thr	Leu Leu	Gln	Pro Phe	His
1250			1255			1260		
Ala Thr	Gly Ala	Glu Ser	Asp	Lys Thr	Glu Lys	Ser	Val Leu	Asn
1265			1270			1275		
Cys Ile	Tyr Lys	Val Leu	His	Gly Cys	Val Tyr	Gly	Ala Gln	Cys
1280			1285			1290		

598

Phe	Ser	Asn	Pro	Arg	Tyr	Phe	Pro	Met	Ser	Leu	Ser	Asp	Leu	Ala
1295						1300					1305			
Ser	Val	Asp	Tyr	Asp	Pro	Phe	Met	His	Leu	Glu	Ser	Leu	Lys	Glu
1310						1315					1320			
Pro	Glu	Pro	Leu	His	Ser	Pro	Asp	Ser	Glu	Arg	Ser	Ser	Lys	Leu
1325						1330					1335			
Gln	Pro	Val	Thr	Glu	Val	Lys	Thr	Gln	Met	Gln	His	Gly	Leu	Ile
1340						1345					1350			
Ser	Ile	Ala	Ala	Arg	Thr	Val	Ile	Thr	His	Leu	Val	Asn	His	Leu
1355						1360					1365			
Gly	His	Tyr	Pro	Met	Ser	Gly	Gly	Pro	Ala	Met	Leu	Thr	Ser	Gln
1370						1375					1380			
Val	Cys	Glu	Asn	His	Asp	Asn	His	Tyr	Ser	Glu	Ser	Thr	Glu	Leu
1385						1390					1395			
Ser	Pro	Glu	Leu	Phe	Glu	Ser	Pro	Asn	Ile	Gln	Phe	Phe	Val	Leu
1400						1405					1410			
Asn	Asn	Thr	Thr	Leu	Val	Ser	Cys	Ile	Gln	Ile	Arg	Ser	Glu	Glu
1415						1420					1425			
Asn	Met	Pro	Gly	Gly	Gly	Leu	Ser	Ala	Gly	Leu	Ala	Ser	Ala	Asn
1430						1435					1440			
Ser	Asn	Val	Arg	Ile	Ile	Val	Arg	Asp	Leu	Ser	Gly	Lys	Tyr	Ser
1445						1450					1455			
Trp	Asp	Ser	Ala	Ile	Leu	Tyr	Gly	Pro	Pro	Pro	Val	Ser	Gly	Leu
1460						1465					1470			
Ser	Glu	Pro	Thr	Ser	Phe	Met	Leu	Ser	Leu	Ser	His	Gln	Glu	Lys
1475						1480					1485			
Pro	Glu	Glu	Pro	Pro	Thr	Ser	Asn	Glu	Cys	Leu	Glu	Asp	Ile	Thr
1490						1495					1500			
Val	Lys	Asp	Gly	Leu	Ser	Leu	Gln	Phe	Lys	Arg	Phe	Arg	Glu	Thr
1505						1510					1515			
Val	Pro	Thr	Trp	Asp	Thr	Ile	Arg	Asp	Glu	Glu	Asp	Val	Leu	Asp

599

1520	1525	1530
Glu Leu Leu Gln Tyr Leu Gly Val Thr Ser Pro Glu Cys Leu Gln		
1535	1540	1545
Arg Thr Gly Ile Ser Leu Asn Ile Pro Ala Pro Gln Pro Val Cys		
1550	1555	1560
Ile Ser Glu Lys Gln Glu Asn Asp Val Ile Asn Ala Ile Leu Lys		
1565	1570	1575
Gln His Thr Glu Glu Lys Glu Phe Val Glu Lys His Phe Asn Asp		
1580	1585	1590
Leu Asn Met Lys Ala Val Glu Gln Asp Glu Pro Ile Pro Gln Lys		
1595	1600	1605
Pro Gln Ser Ala Phe Tyr Tyr Cys Arg Leu Leu Leu Ser Ile Leu		
1610	1615	1620
Gly Met Asn Ser Trp Asp Lys Arg Arg Ser Phe His Leu Leu Lys		
1625	1630	1635
Lys Asn Glu Lys Leu Leu Arg Glu Leu Arg Asn Leu Asp Ser Arg		
1640	1645	1650
Gln Cys Arg Glu Thr His Lys Ile Ala Val Phe Tyr Val Ala Glu		
1655	1660	1665
Gly Gln Glu Asp Lys His Ser Ile Leu Thr Asn Thr Gly Gly Ser		
1670	1675	1680
Gln Ala Tyr Glu Asp Phe Val Ala Gly Leu Gly Trp Glu Val Asn		
1685	1690	1695
Leu Thr Asn His Cys Gly Phe Met Gly Gly Leu Gln Lys Asn Lys		
1700	1705	1710
Ser Thr Gly Leu Thr Thr Pro Tyr Phe Ala Thr Ser Thr Val Glu		
1715	1720	1725
Val Ile Phe His Val Ser Thr Arg Met Pro Ser Asp Ser Asp Asp		
1730	1735	1740
Ser Leu Thr Lys Lys Leu Arg His Leu Gly Asn Asp Glu Val His		
1745	1750	1755

600

Ile Val Trp Ser Glu His Thr Arg Asp Tyr Arg Arg Gly Ile Ile  
 1760 1765 1770

Pro Thr Glu Phe Gly Asp Val Leu Ile Val Ile Tyr Pro Met Lys  
 1775 1780 1785

Asn His Met Phe Ser Ile Gln Ile Met Lys Lys Pro Glu Val Pro  
 1790 1795 1800

Phe Phe Gly Pro Leu Phe Asp Gly Ala Ile Val Asn Gly Lys Val  
 1805 1810 1815

Leu Pro Ile Met Val Arg Ala Thr Ala Ile Asn Ala Ser Arg Ala  
 1820 1825 1830

Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Leu Arg Arg Glu His  
 1835 1840 1845

Asp Ile Phe Lys Cys Cys Trp Phe Tyr Val Val Leu Asp Asn Cys  
 1850 1855 1860

Leu Gln Val Ser Cys Ser His His Leu Glu Pro Thr Thr Phe Glu  
 1865 1870 1875

Asp Phe Ala Ala Gln Val Phe Ser Pro Ala Pro Tyr His His Leu  
 1880 1885 1890

Pro Ser Asp Ala Gly Leu Leu Pro Arg Asp Ser Thr Gln  
 1895 1900 1905

<210> 462

<211> 1889

<212> PRT

<213> Homo sapien

<400> 462

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

601

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu



602

290

295

300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

603

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Val Asn Lys Glu Asp Met Ser Gln Lys Leu  
 660 665 670

Pro Pro Leu Asn Ser Asp Ile Gly Gly Ser Ser Ala Asn Val Pro Asp  
 675 680 685

Leu Met Asp Glu Phe Ile Ala Glu Arg Leu Arg Ser Gly Asn Ala Ser  
 690 695 700

Thr Met Thr Arg Arg Gly Ser Ser Pro Gly Ser Leu Glu Ile Pro Lys  
 705 710 715 720

Asp Leu Pro Asp Ile Leu Asn Lys Gln Asn Gln Met Arg Pro Ile Asp  
 725 730 735

Asp Pro Gly Val Pro Ser Glu Trp Thr Ser Pro Ala Ser Ala Gly Ser  
 740 745 750

Ser Asp Leu Ile Ser Ser Asp Ser His Ser Asp Ser Phe Ser Ala Phe  
 755 760 765

Gln Tyr Asp Gly Arg Lys Phe Asp Asn Phe Gly Phe Gly Thr Asp Thr  
 770 775 780

604

Gly Val Thr Ser Ser Ala Asp Val Asp Ser Gly Ser Gly His His Gln  
785 790 795 800

Ser Ala Glu Glu Gln Glu Val Ala Ser Leu Thr Thr Leu His Ile Asp  
805 810 815

Ser Glu Thr Ser Ser Leu Asn Gln Gln Ala Phe Ser Ala Glu Val Ala  
820 825 830

Thr Ile Thr Gly Ser Glu Ser Ala Ser Pro Val His Ser Pro Leu Gly  
835 840 845

Ser Arg Ser Gln Thr Pro Ser Pro Ser Thr Leu Asn Ile Asp His Met  
850 855 860

Glu Gln Lys Asp Leu Gln Leu Asp Glu Lys Leu His His Ser Val Leu  
865 870 875 880

Gln Thr Pro Asp Asp Leu Glu Ile Ser Glu Phe Pro Ser Glu Cys Cys  
885 890 895

Ser Val Met Ala Gly Gly Thr Leu Thr Gly Trp His Ala Asp Val Ala  
900 905 910

Thr Val Met Trp Arg Arg Met Leu Gly Ile Leu Gly Asp Val Asn Ser  
915 920 925

Ile Met Asp Pro Glu Ile His Ala Gln Val Phe Asp Tyr Leu Cys Glu  
930 935 940

Leu Trp Gln Asn Leu Ala Lys Ile Arg Asp Asn Leu Gly Ile Ser Thr  
945 950 955 960

Asp Asn Leu Thr Ser Pro Ser Pro Pro Val Leu Ile Pro Pro Leu Arg  
965 970 975

Ile Leu Thr Pro Trp Leu Phe Lys Ala Thr Met Leu Thr Asp Lys Tyr  
980 985 990

Lys Gln Gly Lys Leu His Ala Tyr Lys Leu Ile Cys Asn Thr Met Lys  
995 1000 1005

Arg Arg Gln Asp Val Ser Pro Asn Arg Asp Phe Leu Thr His Phe  
1010 1015 1020

605

Tyr Asn Ile Met His Cys Gly Leu Leu His Ile Asp Gln Asp Ile  
 1025 1030 1035

Val Asn Thr Ile Ile Lys His Cys Ser Pro Gln Phe Phe Ser Leu  
 1040 1045 1050

Gly Leu Pro Gly Ala Thr Met Leu Ile Met Asp Phe Ile Val Ala  
 1055 1060 1065

Ala Gly Arg Val Ala Ser Ser Ala Phe Leu Asn Ala Pro Arg Val  
 1070 1075 1080

Glu Ala Gln Val Leu Leu Gly Ser Leu Val Cys Phe Pro Asn Leu  
 1085 1090 1095

Tyr Cys Glu Leu Pro Ser Leu His Pro Asn Ile Pro Asp Val Ala  
 1100 1105 1110

Val Ser Gln Phe Thr Asp Val Lys Glu Leu Ile Ile Lys Thr Val  
 1115 1120 1125

Leu Ser Ser Ala Arg Asp Glu Pro Ser Gly Pro Ala Arg Cys Val  
 1130 1135 1140

Ala Leu Cys Ser Leu Gly Ile Trp Ile Cys Glu Glu Leu Val His  
 1145 1150 1155

Glu Ser His His Pro Gln Ile Lys Glu Ala Leu Asn Val Ile Cys  
 1160 1165 1170

Val Ser Leu Lys Phe Thr Asn Lys Thr Val Ala His Val Ala Cys  
 1175 1180 1185

Asn Met Leu His Met Leu Val His Tyr Val Pro Arg Leu Gln Ile  
 1190 1195 1200

Tyr Gln Pro Asp Ser Pro Leu Lys Ile Ile Gln Ile Leu Ile Ala  
 1205 1210 1215

Thr Ile Thr His Leu Leu Pro Ser Thr Glu Ala Ser Ser Tyr Glu  
 1220 1225 1230

Met Asp Lys Arg Leu Val Val Ser Leu Leu Leu Cys Leu Leu Asp  
 1235 1240 1245

Trp Ile Met Ala Leu Pro Leu Lys Thr Leu Leu Gln Pro Phe His

606

1250	1255	1260
Ala Thr Gly Ala Glu Ser Asp Lys Thr Glu Lys Ser Val Leu Asn		
1265	1270	1275
Cys Ile Tyr Lys Val Leu His Gly Cys Val Tyr Gly Ala Gln Cys		
1280	1285	1290
Phe Ser Asn Pro Arg Tyr Phe Pro Met Ser Leu Ser Asp Leu Ala		
1295	1300	1305
Ser Val Asp Tyr Asp Pro Phe Met His Leu Glu Ser Leu Lys Glu		
1310	1315	1320
Pro Glu Pro Leu His Ser Pro Asp Ser Glu Arg Ser Ser Lys Leu		
1325	1330	1335
Gln Pro Val Thr Glu Val Lys Thr Gln Met Gln His Gly Leu Ile		
1340	1345	1350
Ser Ile Ala Ala Arg Thr Val Ile Thr His Leu Val Asn His Leu		
1355	1360	1365
Gly His Tyr Pro Met Ser Gly Gly Pro Ala Met Leu Thr Ser Gln		
1370	1375	1380
Val Cys Glu Asn His Asp Asn His Tyr Ser Glu Ser Thr Glu Leu		
1385	1390	1395
Ser Pro Glu Leu Phe Glu Ser Pro Asn Ile Gln Phe Phe Val Leu		
1400	1405	1410
Asn Asn Thr Thr Leu Val Ser Cys Ile Gln Ile Arg Ser Glu Glu		
1415	1420	1425
Asn Met Pro Gly Gly Gly Leu Ser Ala Gly Leu Ala Ser Ala Asn		
1430	1435	1440
Ser Asn Val Arg Ile Ile Val Arg Asp Leu Ser Gly Lys Tyr Ser		
1445	1450	1455
Trp Asp Ser Ala Ile Leu Tyr Gly Pro Pro Pro Val Ser Gly Leu		
1460	1465	1470
Ser Glu Pro Thr Ser Phe Met Leu Ser Leu Ser His Gln Glu Lys		
1475	1480	1485

607

Pro	Glu	Glu	Pro	Pro	Thr	Ser	Asn	Glu	Cys	Leu	Glu	Asp	Ile	Thr
1490						1495					1500			
Val	Lys	Asp	Gly	Leu	Ser	Leu	Gln	Phe	Lys	Arg	Phe	Arg	Glu	Thr
1505						1510					1515			
Val	Pro	Thr	Trp	Asp	Thr	Ile	Arg	Asp	Glu	Glu	Asp	Val	Leu	Asp
1520						1525					1530			
Glu	Leu	Leu	Gln	Tyr	Leu	Gly	Val	Thr	Ser	Pro	Glu	Cys	Leu	Gln
1535						1540					1545			
Arg	Thr	Gly	Ile	Ser	Leu	Asn	Ile	Pro	Ala	Pro	Gln	Pro	Val	Cys
1550						1555					1560			
Ile	Ser	Glu	Lys	Gln	Glu	Asn	Asp	Val	Ile	Asn	Ala	Ile	Leu	Lys
1565						1570					1575			
Gln	His	Thr	Glu	Glu	Lys	Glu	Phe	Val	Glu	Lys	His	Phe	Asn	Asp
1580						1585					1590			
Leu	Asn	Met	Lys	Ala	Val	Glu	Gln	Asp	Glu	Pro	Ile	Pro	Gln	Lys
1595						1600					1605			
Pro	Gln	Ser	Ala	Phe	Tyr	Tyr	Cys	Arg	Leu	Leu	Leu	Ser	Ile	Leu
1610						1615					1620			
Gly	Met	Asn	Ser	Trp	Asp	Lys	Arg	Arg	Ser	Phe	His	Leu	Leu	Lys
1625						1630					1635			
Lys	Asn	Glu	Lys	Leu	Leu	Arg	Glu	Leu	Arg	Asn	Leu	Asp	Ser	Arg
1640						1645					1650			
Gln	Cys	Arg	Glu	Thr	His	Lys	Ile	Ala	Val	Phe	Tyr	Val	Ala	Glu
1655						1660					1665			
Gly	Gln	Glu	Asp	Lys	His	Ser	Ile	Leu	Thr	Asn	Thr	Gly	Gly	Ser
1670						1675					1680			
Gln	Ala	Tyr	Glu	Asp	Phe	Val	Ala	Gly	Leu	Gly	Trp	Glu	Val	Asn
1685						1690					1695			
Leu	Thr	Asn	His	Cys	Gly	Phe	Met	Gly	Gly	Leu	Gln	Lys	Asn	Lys
1700						1705					1710			

608

Ser Thr Gly Leu Thr Thr Pro Tyr Phe Ala Thr Ser Thr Val Glu  
 1715 1720 1725

Val Ile Phe His Val Ser Thr Arg Met Pro Ser Asp Ser Asp Asp  
 1730 1735 1740

Ser Leu Thr Lys Lys Leu Arg His Leu Gly Asn Asp Glu Val His  
 1745 1750 1755

Ile Val Trp Ser Glu His Thr Arg Asp Tyr Arg Arg Gly Ile Ile  
 1760 1765 1770

Pro Thr Glu Phe Gly Asp Val Leu Ile Val Ile Tyr Pro Met Lys  
 1775 1780 1785

Asn His Met Phe Ser Ile Gln Ile Met Lys Lys Pro Glu Val Pro  
 1790 1795 1800

Phe Phe Gly Pro Leu Phe Asp Gly Ala Ile Val Asn Gly Lys Val  
 1805 1810 1815

Leu Pro Ile Met Val Arg Ala Thr Ala Ile Asn Ala Ser Arg Ala  
 1820 1825 1830

Leu Lys Ser Leu Ile Pro Leu Tyr Gln Asn Phe Leu Phe Ser Leu  
 1835 1840 1845

Lys Leu Cys Tyr Ser Asn Val Gln Tyr Leu Leu Gln Ser Arg Lys  
 1850 1855 1860

Ala Lys Thr Lys Trp Asn Gly Ile Asp Glu Leu Ile Gly Ser Ala  
 1865 1870 1875

Asn Ala Val Ala Phe Arg Tyr Asn Lys Thr Leu  
 1880 1885

<210> 463

<211> 861

<212> PRT

<213> Homo sapien

<400> 463

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln

609

20

25

30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270



610

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp Glu Gln  
 420 425 430

Met Leu Leu Val Leu Leu Arg Val Thr Glu Ser Val Leu Lys Met Pro  
 435 440 445

Ser Gln Ala Phe Leu Gln Phe Gln Gly Lys Lys Asn Met Thr Leu Ala  
 450 455 460

Gly Arg Leu Ala Gly Pro Leu Phe Gln Thr Leu Ile Val Ala Trp Ile  
 465 470 475 480

Lys Ala Asn Leu Asn Val Tyr Ile Ser Arg Glu Leu Trp Asp Asp Leu  
 485 490 495

Leu Ser Val Leu Ser Ser Leu Thr Tyr Trp Glu Glu Leu Ala Thr Glu  
 500 505 510

611

Trp Ser Leu Thr Met Glu Thr Leu Thr Lys Val Leu Ala Arg Asn Leu  
 515 520 525

Tyr Ser Leu Asp Leu Ser Asp Leu Pro Leu Asp Lys Leu Ser Glu Gln  
 530 535 540

Lys Gln Lys Lys His Lys Gly Lys Gly Val Gly His Glu Phe Gln Lys  
 545 550 555 560

Val Ser Val Asp Lys Ser Phe Ser Arg Gly Trp Ser Arg Asp Gln Pro  
 565 570 575

Gly Gln Ala Pro Met Arg Gln Arg Ser Ala Thr Thr Thr Gly Ser Pro  
 580 585 590

Gly Thr Glu Lys Ala Arg Ser Ile Val Arg Gln Lys Thr Val Asp Ile  
 595 600 605

Asp Asp Ala Gln Ile Leu Pro Arg Ser Thr Arg Val Arg His Phe Ser  
 610 615 620

Gln Ser Glu Glu Thr Gly Asn Glu Val Phe Gly Ala Leu Asn Glu Glu  
 625 630 635 640

Gln Pro Leu Pro Arg Ser Ser Ser Thr Ser Asp Ile Leu Glu Pro Phe  
 645 650 655

Thr Val Glu Arg Ala Lys Gly Ala Val Pro Val Ile Asp Ser Ser Ser  
 660 665 670

Arg His Ala Pro Ser Leu Gln Ser Ser Thr Glu Ala Ser Ser Ile Thr  
 675 680 685

Arg Ser Thr Glu Ser His Ile Thr Asp Thr His Ser Arg Glu Ser Ser  
 690 695 700

Leu Glu Val Gly Asp Ser Ile Tyr Asp His Leu Cys His Leu Ile Gly  
 705 710 715 720

Pro Val Glu Leu Ala Asp Ser Ala Phe Glu Gln Ile Gln Tyr Ile Asp  
 725 730 735

Leu Glu Gly Asp Asp Asp Leu Leu Ser Thr Leu Lys Glu Tyr Phe Lys  
 740 745 750

612

Glu Asn Gln Glu Asn His Ser Lys Asn Glu Thr Gly Lys Asp Pro Ala  
 755 760 765

Ser Gln Glu Val Thr Ile Ala Val Asn Arg Gly Glu Arg Leu Ser Leu  
 770 775 780

Asp Lys Leu Glu Cys Thr Asp Gln Glu Thr Glu Ser Glu Asn Ile Thr  
 785 790 795 800

Ser Phe Val Gly Thr Pro Glu Asn Leu Gln Phe Gln Lys Glu Pro Asn  
 805 810 815

Ser Ala Val Phe Met Ser Asn Ile Ala Pro Asn Gln Ser Asp Ser Phe  
 820 825 830

Phe Arg Thr Gln Thr Ser Glu Lys Ser Lys Gln Leu Asn Thr Asp Lys  
 835 840 845

Gln Pro Ser Glu Pro Ser Leu Asp Ser Pro Cys Asp Lys  
 850 855 860

<210> 464  
 <211> 430  
 <212> PRT  
 <213> Homo sapien

<400> 464

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

613

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys  
 130 135 140

Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu  
 145 150 155 160

Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro  
 165 170 175

Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala  
 180 185 190

Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr  
 195 200 205

Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu  
 210 215 220

Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu  
 225 230 235 240

His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg  
 245 250 255

Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu  
 260 265 270

Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln  
 275 280 285

Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu  
 290 295 300

Glu Ile Val Ile Thr Ser Ser Asp Ile Pro Cys Ile Glu Asn Val Thr  
 305 310 315 320

Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn  
 325 330 335

Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn  
 340 345 350

614

Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu  
 355 360 365

Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Phe Ile Ile  
 370 375 380

Asn Ser Ser Asn Ile Phe Leu Leu Glu Pro Ala Asn Glu Ile Lys Asn  
 385 390 395 400

Leu Leu Asp Glu His Thr Asp Met Cys Lys Arg Ile Leu Asn Ile Tyr  
 405 410 415

Arg Tyr Met Val Val Gln Val Ser Met Asp Lys Lys Thr Trp  
 420 425 430

<210> 465  
 <211> 417  
 <212> PRT  
 <213> Homo sapien

<400> 465

Met Phe Ser Cys Leu Ile Pro Gly Phe Ser Ala Pro Gln Ser Glu His  
 1 5 10 15

Gly Pro Arg Thr Leu Asp Asn Leu Ile Asn Pro Pro Leu Asn Leu Gln  
 20 25 30

Glu Thr Gln Val Thr Ile Glu Glu Ile Thr Pro Leu Val Pro Pro Gln  
 35 40 45

Ser Gly Asp Lys Gly Gln Glu Asp Leu Thr Ser Tyr Phe Leu Glu Ala  
 50 55 60

Leu Leu Lys Tyr Ile Val Ile Gln Val Lys Ser Leu Glu Trp Lys Asn  
 65 70 75 80

Lys Glu Asn Gln Glu Arg Gly Phe Ser Phe Leu Phe Ser His Phe Lys  
 85 90 95

Lys Tyr Tyr Leu Pro Tyr Ile Phe Pro Asn Ile Cys Lys Glu Asn Ser  
 100 105 110

Leu Tyr His Pro Ile Leu Asp Ile Pro Gln Met Arg Pro Lys Pro His  
 115 120 125

Tyr Val Val Ile Lys Lys Asp Ala Glu Thr Asn Glu Ala Ile Tyr Cys

615

130	135	140
Thr Lys Glu Pro Phe Ile Lys Ala Arg Val Ile Val Ile Arg Trp Leu 145 150 155 160		
Val Ser Phe Trp Leu Glu Pro Lys Pro His Thr Gly Pro His Ile Pro 165 170 175		
Gly Met Glu Gly Glu Val Leu Pro Lys Asn Ile Gln Arg Ala Ala Ala 180 185 190		
Ser Leu Val Ser Arg Glu Glu Ser Lys Asn Asp Asn Ala Asp Lys Thr 195 200 205		
Asp Arg Thr Thr Glu Pro Glu Gln Ser His Ser Asn Thr Ser Thr Leu 210 215 220		
Thr Glu Arg Glu Pro Ser Ser Ser Ser Leu Cys Ser Ile Asp Glu Glu 225 230 235 240		
His Leu Thr Asp Ile Glu Ile Val Arg Arg Val Phe Ser Ser Lys Arg 245 250 255		
Ser Asn Val Asn Phe Val Thr Glu Ile Phe Arg Gln Ala Phe Leu Leu 260 265 270		
Pro Ile Cys Glu Ala Ala Ala Met Arg Lys Val Val Lys Val Tyr Gln 275 280 285		
Glu Trp Ile Gln Gln Glu Glu Lys Pro Leu Phe Met Gln Glu Pro Glu 290 295 300		
Glu Ile Val Ile Thr Ser Ser Asp Leu Pro Cys Ile Glu Asn Val Thr 305 310 315 320		
Asp His Asp Ile Ser Met Glu Glu Gly Glu Lys Arg Glu Glu Glu Asn 325 330 335		
Gly Thr Asn Thr Ala Asp His Val Arg Asn Ser Ser Trp Ala Lys Asn 340 345 350		
Gly Ser Tyr Gln Gly Ala Leu His Asn Ala Ser Glu Glu Ala Thr Glu 355 360 365		
Gln Asn Ile Arg Ala Gly Thr Gln Ala Val Leu Gln Val Asp His Phe 370 375 380		

616

Met Ala Ile Phe Lys Asn Lys Ile Ile Ile Lys Tyr Phe Cys Ser Val  
 385 390 395 400

Phe Gln Tyr Thr Val Tyr Phe Ser Gln Tyr Asn Lys Phe Thr Thr Tyr  
 405 410 415

Ile

<210> 466  
 <211> 76  
 <212> PRT  
 <213> Homo sapien

<400> 466

Met Asn Arg Phe Lys Glu Gly Phe Lys Asn Ser Trp Ile Thr His Pro  
 1 5 10 15

Pro Trp Thr Ile Ile Gly Ser Gln Arg Ser Gly Ala Tyr His Lys Ala  
 20 25 30

His Arg Ala Ala Ser Met Lys Asn Ala Ser Thr Asn Gly Cys Pro Leu  
 35 40 45

Ser Glu Thr Glu Tyr Trp Ala Arg Arg Asp Pro Ile Pro Ala Asn Gly  
 50 55 60

Ala Phe Leu Arg Leu Ser Arg His Lys Thr Ser His  
 65 70 75

<210> 467  
 <211> 198  
 <212> PRT  
 <213> Homo sapien

<400> 467

Met Phe Lys Asn Thr Phe Gln Ser Gly Phe Leu Ser Ile Leu Tyr Ser  
 1 5 10 15

Ile Gly Ser Lys Pro Leu Gln Ile Trp Asp Lys Lys Val Arg Asn Gly  
 20 25 30

His Ile Lys Arg Ile Thr Asp Asn Asp Ile Gln Ser Leu Val Leu Glu  
 35 40 45

Ile Glu Gly Thr Asn Val Ser Thr Thr Tyr Ile Thr Cys Pro Ala Asp

617

50

55

60

Pro Lys Lys Thr Leu Gly Ile Lys Leu Pro Phe Leu Val Met Ile Ile  
 65 70 75 80

Lys Asn Leu Lys Lys Tyr Phe Thr Phe Glu Val Gln Val Leu Asp Asp  
 85 90 95

Lys Asn Val Arg Arg Arg Phe Arg Ala Ser Asn Tyr Gln Ser Thr Thr  
 100 105 110

Arg Val Lys Pro Phe Ile Cys Thr Met Pro Met Arg Leu Asp Asp Gly  
 115 120 125

Trp Asn Gln Ile Gln Phe Asn Leu Leu Asp Phe Thr Arg Arg Ala Tyr  
 130 135 140

Gly Thr Asn Tyr Ile Glu Thr Leu Arg Val Gln Asn Pro Ser Leu Arg  
 145 150 155 160

Gln Ala Lys Glu Met Pro Glu Met Thr Arg Phe Gln Ser Trp Lys Arg  
 165 170 175

Ala Ser Arg Arg Phe Arg Lys Arg Gly Arg Thr Val Thr Phe Arg Leu  
 180 185 190

Ser Lys Glu Ala Leu Pro  
 195

<210> 468  
 <211> 266  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> MISC\_FEATURE  
 <222> (18)..(18)  
 <223> x= any amino acid

<400> 468

Met Ile Gln Val Gly Cys Arg Leu Thr Glu Asp Pro Trp Asp Leu Leu  
 1 5 10 15

Thr Xaa Ala Arg Phe Cys Gln Cys Ile Pro Ala Glu Leu Arg Gln Asp  
 20 25 30

Ala Leu Cys Ala Leu Ser Arg Thr Ser Val Leu Arg Ile Gly Asn Leu



618

35

40

45

His Ile Thr Gly Val Leu Arg Ser Ser Ile Gln Trp Gly Ile Val Ser  
 50 55 60

Asn Glu Glu Gly Arg Pro Glu His His Val Leu Lys Leu Arg Ser Gln  
 65 70 75 80

His Gly Phe Leu Ser Ile Leu Tyr Ser Ile Gly Ser Lys Pro Leu Gln  
 85 90 95

Ile Trp Asp Lys Lys Val Arg Asn Gly His Ile Lys Arg Ile Thr Asp  
 100 105 110

Asn Asp Ile Gln Ser Leu Val Leu Glu Ile Glu Gly Thr Asn Val Ser  
 115 120 125

Thr Thr Tyr Ile Thr Cys Pro Ala Asp Pro Lys Lys Thr Leu Gly Ile  
 130 135 140

Lys Leu Pro Phe Leu Val Met Ile Ile Lys Asn Leu Lys Lys Tyr Phe  
 145 150 155 160

Thr Phe Glu Val Gln Val Leu Asp Asp Lys Asn Val Arg Arg Arg Phe  
 165 170 175

Arg Ala Ser Asn Tyr Gln Ser Thr Thr Arg Val Lys Pro Phe Ile Cys  
 180 185 190

Thr Met Pro Met Arg Leu Asp Asp Gly Trp Asn Gln Ile Gln Phe Asn  
 195 200 205

Leu Leu Asp Phe Thr Arg Arg Ala Tyr Gly Thr Asn Tyr Ile Glu Thr  
 210 215 220

Leu Arg Val Gln Ile His Ala Asn Cys Arg Ile Arg Arg Val Tyr Phe  
 225 230 235 240

Ser Asp Arg Leu Tyr Ser Glu Asp Glu Leu Pro Ala Glu Phe Lys Leu  
 245 250 255

Tyr Leu Pro Val Gln Asn Lys Ala Lys Gln  
 260 265

&lt;210&gt; 469

&lt;211&gt; 250

619

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 469

Met Phe Lys Asn Thr Phe Gln Ser Gly Phe Leu Ser Ile Leu Tyr Ser  
 1 5 10 15

Ile Gly Ser Lys Pro Leu Gln Ile Trp Asp Lys Lys Val Arg Asn Gly  
 20 25 30

His Ile Lys Arg Ile Thr Asp Asn Asp Ile Gln Ser Leu Val Leu Glu  
 35 40 45

Ile Glu Gly Thr Asn Val Ser Thr Thr Tyr Ile Thr Cys Pro Ala Asp  
 50 55 60

Pro Lys Lys Thr Leu Gly Ile Lys Leu Pro Phe Leu Val Met Ile Ile  
 65 70 75 80

Lys Asn Leu Lys Lys Tyr Phe Thr Phe Glu Val Gln Val Leu Asp Asp  
 85 90 95

Lys Asn Val Arg Arg Arg Phe Arg Ala Ser Asn Tyr Gln Ser Thr Thr  
 100 105 110

Arg Val Lys Pro Phe Ile Cys Thr Met Pro Met Arg Leu Asp Asp Gly  
 115 120 125

Trp Asn Gln Ile Gln Phe Asn Leu Leu Asp Phe Thr Arg Arg Ala Tyr  
 130 135 140

Gly Thr Asn Tyr Ile Glu Thr Leu Arg Val Gln Ile His Ala Asn Cys  
 145 150 155 160

Arg Ile Arg Arg Val Tyr Phe Ser Asp Arg Leu Tyr Ser Glu Asp Glu  
 165 170 175

Leu Pro Ala Glu Phe Lys Leu Tyr Leu Pro Val Gln Asn Lys Ala Lys  
 180 185 190

Val Ser Gln Ser Ser Pro Glu Glu Gly Pro Pro Val Ser Gly Gly Ser  
 195 200 205

Cys Val Pro Gly Arg Cys Ser Gly Leu Arg Ile Gln Leu Gln Ser Leu  
 210 215 220

620

Ser Val Leu Thr Leu Trp Gly Ala Phe Ile Ser Gln Asp Leu Arg Ser  
 225 230 235 240

Pro Ser Ser Thr Glu Ser Gly Met Leu Leu  
 245 250

<210> 470  
 <211> 88  
 <212> PRT  
 <213> Homo sapien

<400> 470

Met Gln Ile Val Ala Ser Asp Gly Phe Thr Ser Gln Thr Asp Ser Thr  
 1 5 10 15

Gln Lys Met Ser Cys Arg Gln Ser Ser Asn Cys Ile Ser Gln Phe Arg  
 20 25 30

Thr Arg Gln Ser Asn Asn Trp Asn Cys Asp Ser Arg Asp Arg Pro Leu  
 35 40 45

Asp Val Thr Leu Leu Phe Lys Arg Lys Leu Cys Gly Gly Arg Cys Lys  
 50 55 60

Asn Ile Phe Ile Leu Val Cys Ser Ala Val Val Leu Leu Phe Ile Leu  
 65 70 75 80

Gly Val Ala Cys His Gly His Arg  
 85

<210> 471  
 <211> 173  
 <212> PRT  
 <213> Homo sapien

<400> 471

Met Phe Lys Asn Thr Phe Gln Ser Gly Phe Leu Ser Ile Leu Tyr Ser  
 1 5 10 15

Ile Gly Ser Lys Pro Leu Gln Ile Trp Asp Lys Lys Val Arg Asn Gly  
 20 25 30

His Ile Lys Arg Ile Thr Asp Asn Asp Ile Gln Ser Leu Val Leu Glu  
 35 40 45

Ile Glu Gly Thr Asn Val Ser Thr Thr Tyr Ile Thr Cys Pro Ala Asp  
 50 55 60

621

Pro Lys Lys Thr Leu Gly Ile Lys Leu Pro Phe Leu Val Met Ile Ile  
65 70 75 80

Lys Asn Leu Lys Lys Tyr Phe Thr Phe Glu Val Gln Val Leu Asp Asp  
85 90 95

Lys Asn Val Arg Arg Arg Phe Arg Ala Ser Asn Tyr Gln Ser Thr Thr  
100 105 110

Arg Val Lys Pro Phe Ile Cys Thr Met Pro Met Arg Leu Asp Asp Gly  
115 120 125

Trp Asn Gln Ile Gln Phe Asn Leu Leu Asp Phe Thr Arg Arg Ala Tyr  
130 135 140

Gly Thr Asn Tyr Ile Glu Thr Leu Arg Val Gln Val Leu Leu Leu Ser  
145 150 155 160

Gln Ile Glu Pro Trp Val Gly Asp Arg Ala His Cys Val  
165 170

<210> 472

<211> 110

<212> PRT

<213> Homo sapien

<400> 472

Met Ala Thr Ser Lys Glu Ser Leu Ile Val Leu Asp Asp Lys Asn Val  
1 5 10 15

Arg Arg Arg Phe Arg Ala Ser Asn Tyr Gln Ser Thr Thr Arg Val Lys  
20 25 30

Pro Phe Ile Cys Thr Met Pro Met Arg Leu Asp Asp Gly Trp Asn Gln  
35 40 45

Ile Gln Phe Asn Leu Leu Asp Phe Thr Arg Arg Ala Tyr Gly Thr Asn  
50 55 60

Tyr Ile Glu Thr Leu Arg Val Gln Ile His Ala Asn Cys Arg Ile Arg  
65 70 75 80

Arg Val Tyr Phe Ser Asp Arg Leu Tyr Ser Glu Asp Glu Leu Pro Ala  
85 90 95

Glu Phe Lys Leu Tyr Leu Pro Val Gln Asn Lys Ala Lys Gln

622

100

105

110

<210> 473  
 <211> 25  
 <212> PRT  
 <213> Homo sapien

<400> 473

Met Arg Leu Asn Thr Phe Tyr Thr Thr Tyr Gln Lys Pro Gln Lys Ser  
 1 5 10 15

Tyr Gly Asn Asn Gly Met Asn Thr Gln  
 20 25

<210> 474  
 <211> 50  
 <212> PRT  
 <213> Homo sapien

<400> 474

Met Cys Phe Cys Phe Pro Gln Glu Glu Asn His Val Asp Ser Gln Phe  
 1 5 10 15

Thr Met Ser Gln Pro Val Cys Lys Ile Phe Tyr Ile Met Gly Lys Phe  
 20 25 30

Ile Val Thr Gln Lys Phe Ser Val Phe Ser Leu Ser Tyr Gln Lys Leu  
 35 40 45

Gln Met  
 50

<210> 475  
 <211> 90  
 <212> PRT  
 <213> Homo sapien

<400> 475

Met Leu Lys Tyr Phe Leu Ser Val Trp Trp Ser Leu Glu Val Asn Ser  
 1 5 10 15

His Ala Arg Arg Arg His Gln Lys Ala Trp Gly Ser Ser Asp Arg Val  
 20 25 30

Gly Ala Cys Trp Leu Thr Gly Gly Leu His Arg Arg Val Ile Arg Leu  
 35 40 45

Glu Asn Phe Leu Arg Ile Pro Arg Thr Glu Ser Leu Thr Ser Phe Phe

623

50

55

60

Phe Ser Phe Phe Phe Val Phe Arg Ser Val Ala Gln Ala Glu Val Ser  
 65 70 75 80

Leu Lys Ser Ala Phe Lys Ala Leu Leu Arg  
 85 90

&lt;210&gt; 476

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 476

Met Met Leu Tyr Phe Leu Leu Ile Phe Glu Tyr Leu Phe Trp Phe His  
 1 5 10 15

Phe Lys Trp Leu Leu Ser Glu Ala Val Leu Gly Ile Gln Ser Asp Ser  
 20 25 30

Ile Val Thr Leu Met Arg Leu Lys Phe Gln Gly His Ser Leu Ala Trp  
 35 40 45

Val Leu Ser Lys Ala Leu Gly Gly Pro  
 50 55

&lt;210&gt; 477

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 477

Met Leu Gln Gly Gln Leu Ser Leu His Arg Asn Lys Thr Thr Ile Ala  
 1 5 10 15

Phe Gln Gly His Gln Ser Phe Leu Gln Asn Glu Asn Lys Val Ser Pro  
 20 25 30

Ala Tyr Leu Asn Ser Pro Asn Thr Leu Gly Asp Leu Ile Leu Ile Ser  
 35 40 45

Ser Val Phe His Ser Asp Lys Ser Ile Gln Ser Leu Val Asn Phe Tyr  
 50 55 60

Ser Ala  
 65

624

<210> 478  
 <211> 16  
 <212> PRT  
 <213> Homo sapien

<400> 478

Met Phe Gly Glu Val Phe Arg Val Gln Ile Ile Phe Ile Phe Glu Leu  
 1 5 10 15

<210> 479  
 <211> 152  
 <212> PRT  
 <213> Homo sapien

<400> 479

Met Trp Pro Thr Gly Pro Gly Pro Ser Val Arg Lys Glu Gln Ala Arg  
 1 5 10 15

Pro Pro Ala Arg Arg Asn His Gln Val Gly His Leu Pro Tyr Arg His  
 20 25 30

Pro Glu Val Pro Val Asp Ile Lys Thr Ser Ala Pro Ser Glu Ala Pro  
 35 40 45

Gly Leu Arg Ser Gly Gln Arg Gly Gly Arg Gly Gln Gly Glu Gly Ala  
 50 55 60

Ala Lys Glu Arg Arg Thr Ala Arg Gly Gly Gln Gly Ala Ser Leu Pro  
 65 70 75 80

Arg Gln Gly Pro Pro Gln Pro Ser Arg Arg Leu Asp Arg Gly Ile Val  
 85 90 95

Leu Arg Arg Arg Pro Ser Ser Gly Pro Ala Pro Ala Pro Pro Arg Ala  
 100 105 110

Cys Tyr Trp Arg Lys Val Pro Gly Arg Ala Ala Thr Gly Arg His Ala  
 115 120 125

Ala Gly Pro Ala Pro Phe Pro Thr Ser Ser Lys Ala Ala Pro Ala Leu  
 130 135 140

Gly Leu Arg Gly Arg Arg Ser Gly  
 145 150

<210> 480  
 <211> 365  
 <212> PRT

625

&lt;213&gt; Homo sapien

&lt;400&gt; 480

Met Trp Pro Thr Gly Pro Gly Pro Ser Val Arg Lys Glu Gln Ala Arg  
 1 5 10 15

Pro Pro Ala Arg Arg Asn His Gln Val Gly His Leu Pro Tyr Arg His  
 20 25 30

Pro Glu Val Pro Val Asp Ile Lys Thr Ser Ala Pro Ser Glu Ala Pro  
 35 40 45

Gly Leu Arg Ser Gly Gln Arg Gly Gly Arg Gly Gln Gly Glu Gly Ala  
 50 55 60

Ala Lys Glu Arg Arg Thr Ala Arg Gly Gly Gln Gly Ala Ser Leu Pro  
 65 70 75 80

Arg Gln Gly Pro Pro Gln Pro Ser Arg Arg Leu Asp Arg Gly Ile Val  
 85 90 95

Leu Arg Arg Arg Pro Ser Ser Gly Pro Ala Pro Ala Pro Pro Arg Ala  
 100 105 110

Cys Tyr Trp Arg Lys Val Pro Gly Arg Ala Ala Thr Gly Arg His Ala  
 115 120 125

Ala Gly Pro Ala Pro Phe Pro Thr Arg Ser Lys Ala Ala Pro Ala Leu  
 130 135 140

Gly Leu Arg Gly Arg Arg Ser Gly Arg Gly Leu Gly Gly Phe Ala Gly  
 145 150 155 160

Ala Gly Gly Gly Glu Ser Pro Asp Ser Pro Asp Ala Ala Arg Arg Ala  
 165 170 175

Met Gly Phe Pro Ala Ala Ala Leu Leu Cys Ala Leu Cys Cys Gly Leu  
 180 185 190

Leu Ala Pro Ala Ala Arg Ala Gly Tyr Ser Glu Glu Arg Cys Ser Trp  
 195 200 205

Arg Gly Ser Gly Leu Thr Gln Glu Pro Gly Ser Val Gly Gln Leu Ala  
 210 215 220

Leu Ala Cys Ala Glu Gly Ala Val Glu Trp Leu Tyr Pro Ala Gly Ala



626

225					230					235					240
Leu	Arg	Leu	Thr	Leu	Gly	Gly	Pro	Asp	Pro	Arg	Ala	Arg	Pro	Gly	Ile
				245					250					255	
Ala	Cys	Leu	Arg	Pro	Val	Arg	Pro	Phe	Ala	Gly	Ala	Gln	Val	Phe	Ala
			260					265					270		
Glu	Arg	Ala	Gly	Gly	Ala	Leu	Glu	Leu	Leu	Leu	Ala	Glu	Gly	Pro	Gly
		275					280					285			
Pro	Ala	Gly	Gly	Arg	Cys	Val	Arg	Trp	Gly	Pro	Arg	Glu	Arg	Arg	Ala
	290					295					300				
Leu	Phe	Leu	Gln	Ala	Thr	Pro	His	Gln	Asp	Ile	Ser	Arg	Arg	Val	Ala
305					310					315					320
Ala	Phe	Arg	Phe	Glu	Leu	Arg	Glu	Asp	Gly	Arg	Pro	Glu	Leu	Pro	Pro
				325					330					335	
Gln	Ala	His	Gly	Leu	Gly	Val	Asp	Gly	Ala	Cys	Arg	Pro	Cys	Ser	Asp
			340					345					350		
Ala	Glu	Leu	Leu	Leu	Ala	Ala	Cys	Thr	Ser	Asp	Phe	Gly			
		355					360					365			
<210>	481														
<211>	332														
<212>	PRT														
<213>	Homo sapien														
<400>	481														
Met	Gly	Phe	Pro	Ala	Ala	Ala	Leu	Leu	Cys	Ala	Leu	Cys	Cys	Gly	Leu
1				5					10					15	
Leu	Ala	Pro	Ala	Ala	Arg	Ala	Gly	Tyr	Ser	Glu	Glu	Arg	Cys	Ser	Trp
			20					25					30		
Arg	Gly	Ser	Gly	Leu	Thr	Gln	Glu	Pro	Gly	Ser	Val	Gly	Gln	Leu	Ala
		35					40					45			
Leu	Ala	Cys	Ala	Glu	Gly	Ala	Val	Glu	Trp	Leu	Tyr	Pro	Ala	Gly	Ala
	50					55					60				
Leu	Arg	Leu	Thr	Leu	Gly	Gly	Pro	Asp	Pro	Arg	Ala	Arg	Pro	Gly	Ile
65					70					75					80

627

Ala Cys Leu Arg Pro Val Arg Pro Phe Ala Gly Ala Gln Val Phe Ala  
                                   85                                  90                                  95

Glu Arg Ala Gly Gly Ala Leu Glu Leu Leu Leu Ala Glu Gly Pro Gly  
                                   100                                  105                                  110

Pro Ala Gly Gly Arg Cys Val Arg Trp Gly Pro Arg Glu Arg Arg Ala  
                                   115                                  120                                  125

Leu Phe Leu Gln Ala Thr Pro His Gln Asp Ile Ser Arg Arg Val Ala  
                                   130                                  135                                  140

Ala Phe Arg Phe Glu Leu Arg Glu Asp Gly Arg Pro Glu Leu Pro Pro  
                                   145                                  150                                  155                                  160

Gln Ala His Gly Leu Gly Val Asp Gly Ala Cys Arg Pro Cys Ser Asp  
                                   165                                  170                                  175

Ala Glu Leu Leu Leu Ala Ala Cys Thr Ser Asp Phe Gly Glu Gly Gly  
                                   180                                  185                                  190

Ala His Cys Phe Gly Gly Asp Gly Thr Ile Asn Lys Asn Ser Val His  
                                   195                                  200                                  205

Ala Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys  
                                   210                                  215                                  220

Lys Gly Gly Arg Lys Lys Asn Thr Pro Glu Gly Gly Pro Lys Lys Ser  
                                   225                                  230                                  235                                  240

Glu Asn Pro Asn Val Cys Met Val His Lys Glu Gly Asp Asp Gln Lys  
                                   245                                  250                                  255

Glu Arg Asn Gly Asn Ile Lys Ala Asn Gly Arg Lys Glu Arg Thr Val  
                                   260                                  265                                  270

Thr Thr His Arg Ser Lys Ser Glu Lys Lys Val His Lys Gln Glu Glu  
                                   275                                  280                                  285

Thr Ile Gly Glu Arg Asn Thr Asn Asn Gly Gly Gly Glu Arg Asn Ala  
                                   290                                  295                                  300

Asn Lys Ser Thr Lys Thr Lys Tyr Tyr Ser Thr Lys Lys Glu Asn Tyr  
                                   305                                  310                                  315                                  320

628

Met Lys Thr Arg Ile Glu Gly Gly Arg Lys Asn Ile  
 325 330

<210> 482  
 <211> 84  
 <212> PRT  
 <213> Homo sapien

<400> 482

Met Gln Gly Arg Leu Leu Pro Leu Pro Asp Ile Ser Phe Trp Ala Cys  
 1 5 10 15

Ser Phe Ser Pro Thr Phe Ser Leu Thr Ser Phe Lys Ser Tyr Glu Val  
 20 25 30

Pro Phe Lys Thr Ser Tyr Ser Leu Lys Pro Ser Leu Tyr Gln Phe Asp  
 35 40 45

Leu Ala Ser Ile Gly Thr Glu Lys Ser Gly Asn Glu Arg Cys Asp Cys  
 50 55 60

Lys Leu Ile Trp Gln Lys Glu Glu Asp Ser Cys Val Gln Lys Ser Leu  
 65 70 75 80

Trp Leu Thr Glu

<210> 483  
 <211> 46  
 <212> PRT  
 <213> Homo sapien

<400> 483

Met Cys Thr Thr Val Met Gly Pro Glu Leu Gly Pro Leu Trp Gly Glu  
 1 5 10 15

Trp Thr Leu Ser Trp Gly Ser His Leu Trp Asp Thr Lys Lys Leu Ser  
 20 25 30

Ser Glu His Asp Val Leu Thr Arg Tyr Val Lys Lys Ser Lys  
 35 40 45

<210> 484  
 <211> 65  
 <212> PRT  
 <213> Homo sapien

<400> 484

629

Cys Ile Asn Phe Asp Phe Leu Thr Tyr Arg Val Lys Thr Ser Cys Ser  
 1 5 10 15

Leu Leu Ser Phe Leu Val Ser His Lys Trp Asp Pro Gln Leu Ser Val  
 20 25 30

His Ser Pro His Ser Gly Pro Ser Ser Gly Pro Met Thr Val Val His  
 35 40 45

Ile Ala Lys Glu Gln His Gly Ser Gly Pro Gln Thr Leu Pro Gln Pro  
 50 55 60

Cys  
 65

<210> 485  
 <211> 54  
 <212> PRT  
 <213> Homo sapien

<400> 485

Met Ser His Ser Glu Ile Leu Ile Ser Leu Gln Arg Ala Arg Lys Lys  
 1 5 10 15

Leu Pro Thr Leu His Pro Ile Phe Ser Val Cys Val Lys Ser Pro Val  
 20 25 30

Lys Gln Asp Ile Ala Ala Gln Phe Arg Asn Val Lys His Val Thr Met  
 35 40 45

Ile Gln Glu Leu Pro Ile  
 50

<210> 486  
 <211> 40  
 <212> PRT  
 <213> Homo sapien

<400> 486

Met Pro Thr Asn Gln Leu Leu Val Ala Pro Val Asn Thr Pro Cys Phe  
 1 5 10 15

Pro Leu Glu Arg Leu Leu Tyr Cys Ile Trp Cys Gln Cys Leu Arg Lys  
 20 25 30

Gln Gln Tyr Gln Pro Pro Leu His  
 35 40

630

<210> 487  
 <211> 50  
 <212> PRT  
 <213> Homo sapien

<400> 487

Met Val Val Lys His Phe Lys Asp Thr Ser Ile Leu Gly Leu Cys Ser  
 1 5 10 15

Pro Glu Ser Ser Leu His Ile Phe Pro Thr Ile Gln Pro His Gln Glu  
 20 25 30

Met Ile Thr Ala Gln Lys Val Tyr Gln Tyr Leu Pro Lys Leu Met Asp  
 35 40 45

Leu Lys  
 50

<210> 488  
 <211> 60  
 <212> PRT  
 <213> Homo sapien

<400> 488

Met Lys Val Cys Phe Ala Ala Ala Thr Ala His Leu Leu Arg Pro Leu  
 1 5 10 15

Gln Gln Arg Leu Ser Thr Ile Leu Gly Lys Leu Gly Gly Ala Lys Val  
 20 25 30

His Gly Ser Ser Gly Thr Ser His Thr Arg Ile Cys Leu Met Glu Val  
 35 40 45

Thr Gln Gly Gly Arg Asn Glu Gln Phe Ile Leu His  
 50 55 60

<210> 489  
 <211> 67  
 <212> PRT  
 <213> Homo sapien

<400> 489

Met Asn Arg Leu Trp Tyr Trp Phe Glu Glu Ile Lys Ser Leu Asn Gly  
 1 5 10 15

Leu Lys Glu Ile Ile Leu Leu Ile Cys Gln Asn Pro Cys Phe Gln Arg  
 20 25 30

631

Arg Leu Thr Thr Gly Ser Leu Trp Lys Leu Ile Ile Lys Cys Ile Leu  
 35 40 45

Leu Tyr Ile Lys Pro Phe His Ala Ala Asn Thr Thr Ile Tyr Phe Cys  
 50 55 60

Asn Ile Asn  
 65

<210> 490  
 <211> 19  
 <212> PRT  
 <213> Homo sapien

<400> 490

Met Phe Phe Lys Leu Leu Ser Asn Glu Cys Thr Val Lys Ser Lys Ile  
 1 5 10 15

Asn Gln Val

<210> 491  
 <211> 26  
 <212> PRT  
 <213> Homo sapien

<400> 491

Met Thr Ala Tyr Ser Ser Thr Leu Lys Thr Ser Thr Phe Phe Phe Leu  
 1 5 10 15

Gly Leu Ser Glu Leu Thr Arg Thr Asn Gln  
 20 25

<210> 492  
 <211> 156  
 <212> PRT  
 <213> Homo sapien

<400> 492

Met Lys Gly Leu Asp Trp Val Asn Thr Glu Pro Pro Pro Glu Ser Glu  
 1 5 10 15

Ser Leu Leu Ser Val Asp Leu Pro Asp Leu Gly Trp Leu Cys Trp Tyr  
 20 25 30

Ser His Phe Leu Leu His Ile Tyr Leu Pro Leu Val Ser His Ile Val  
 35 40 45

632

Ser Cys Met Ser Cys Cys Pro Arg Ala Leu Thr Gly Thr Pro Ile Ile  
50 55 60

Asn Ser Cys Pro Cys Ser Gly His Gly Gly Pro Ala Trp Leu Gly Gln  
65 70 75 80

Thr Gln Trp Pro Val Gly Ala Arg Ala Pro Pro Ser Arg Thr Gly Gln  
85 90 95

Arg Ser Gln Pro Gln Gly Gln Gly Lys Ala Ser Ala Pro Thr Val Ala  
100 105 110

Thr Ser Ser Arg Pro Ser Thr Phe Leu Arg Leu Ile Trp Arg Pro Ala  
115 120 125

Pro Leu Asp Ser Ala Leu Pro Pro Arg Lys Gln His Pro Glu Leu Arg  
130 135 140

Ala Glu Glu Leu Gln Gly Leu Gly Thr Gly Pro Ala  
145 150 155

<210> 493

<211> 156

<212> PRT

<213> Homo sapien

<400> 493

Met Lys Gly Leu Asp Trp Val Asn Thr Glu Pro Pro Pro Glu Ser Glu  
1 5 10 15

Ser Leu Leu Ser Val Asp Leu Pro Asp Leu Gly Trp Leu Cys Trp Tyr  
20 25 30

Ser His Phe Leu Leu His Ile Tyr Leu Pro Leu Val Ser His Ile Val  
35 40 45

Ser Cys Met Ser Cys Cys Pro Arg Ala Leu Thr Gly Thr Pro Ile Ile  
50 55 60

Asn Ser Cys Pro Cys Ser Gly His Gly Gly Pro Ala Trp Leu Gly Gln  
65 70 75 80

Thr Gln Trp Pro Val Gly Ala Arg Ala Pro Pro Ser Arg Thr Gly Gln  
85 90 95

Arg Ser Gln Pro Gln Gly Gln Gly Lys Ala Ser Ala Pro Thr Val Ala

633

100

105

110

Thr Ser Ser Arg Pro Ser Thr Phe Leu Arg Leu Ile Trp Arg Pro Ala  
 115 120 125

Pro Leu Asp Ser Ala Leu Pro Pro Arg Lys Gln His Pro Glu Leu Arg  
 130 135 140

Ala Glu Glu Leu Gln Gly Leu Gly Thr Gly Pro Ala  
 145 150 155

<210> 494  
 <211> 39  
 <212> PRT  
 <213> Homo sapien

<400> 494

Met Gln Arg Gln Val Gly Arg Thr Gly Leu Leu Trp Ser Ser Val Ser  
 1 5 10 15

Leu Leu Pro Trp Pro Leu Leu Pro Leu Cys Ser Gly Leu Leu Gly Arg  
 20 25 30

Gly Leu Leu Ser Lys Ala Gly  
 35

<210> 495  
 <211> 43  
 <212> PRT  
 <213> Homo sapien

<400> 495

Met Thr Asn Tyr Tyr Ser Thr Gly Ile Leu Phe Leu Ile Asp Phe Pro  
 1 5 10 15

Lys Lys Leu His Val Cys Val Phe Phe Ser Val Ile His Leu Ser His  
 20 25 30

Lys Met Lys Ser Ala Cys Ser His Leu Pro Gln  
 35 40

<210> 496  
 <211> 94  
 <212> PRT  
 <213> Homo sapien

<400> 496

Met Gln Lys Arg Pro Gln Ile Glu Ser Arg Cys Leu Gly Pro Leu Leu



634

1				5						10						15
Pro	Gln	Gly	Leu	Leu	Pro	Thr	Glu	Gly	Pro	Met	Asp	His	Phe	Pro	Leu	
			20					25					30			
Asn	Ala	Ser	Thr	Arg	Thr	Ala	Trp	Val	Ala	Asp	Ile	Asp	Gly	Asp	Ala	
		35					40					45				
Gln	Ser	Ser	Trp	Pro	Arg	Trp	Gly	Thr	Glu	Pro	Gln	Ala	Val	Ala	Arg	
	50					55					60					
Gln	Pro	Leu	Arg	Pro	Arg	Phe	Arg	Lys	Val	Pro	Leu	Leu	Pro	Arg	Arg	
65					70					75					80	
Asn	Val	Arg	Glu	Arg	Pro	Gly	Gly	Trp	Ala	Met	Leu	Val	Val			
				85					90							

<210>	497
<211>	62
<212>	PRT
<213>	Homo sapien

<400> 497

Met Asp Gly Gly Lys Gln Met Asn Lys Asn Gly Glu Glu Arg Gly Leu  
1 5 10 15

Glu Ala Thr Ala Tyr Pro Ala Thr Ser Trp Ala Thr Thr His Arg Pro  
20 25 30

Ile Leu Glu His Ile Ser Val Thr His Arg Val Asn Gly Ile Ile Pro  
35 40 45

Cys Glu Leu Ser Ala Ser Leu Lys Leu His Pro Ser Ala His  
50 55 60

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<210> 498
<211> 43
<212> PRT
<213> Homo sapien
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<400> 498

Leu Asp Ser Gln Pro His Leu Trp Ser Pro Arg Pro Leu Ser His Arg  
1 5 10 15

Arg Cys Tyr Gly Ser Leu Asn Glu Arg Thr Arg Asp Ser Val His His  
20 25 30

635

Val Ala Leu Asp Leu Ala Leu Val Leu Arg Leu  
           35                          40

<210> 499  
 <211> 100  
 <212> PRT  
 <213> Homo sapien

<400> 499

Met Glu His Asn Tyr Gln Gln Gly Val Gly Met Glu Lys Leu Lys Leu  
 1                          5                          10                          15

Pro Met Phe Phe Gln Ser Asn Asn Asn Pro Ser Leu Ala Ile Ser Trp  
                           20                          25                          30

Thr Leu Asn Val Ser Lys Tyr Asn Met Lys Lys Lys Asn Leu Ser His  
           35                          40                          45

His Ala Gln Pro Thr Pro Trp Cys Ile Asp Leu Leu Ser Ala Ser Gly  
           50                          55                          60

Asn Gly Cys Gly His Asn Val Val Ser Trp Glu Ser Ser Cys Ile Gln  
 65                          70                          75                          80

Gly Ile Val Met Arg Glu Arg Leu Val Asn Arg Ile Gly Val His Leu  
                           85                          90                          95

Pro Trp His Ser  
                           100

<210> 500  
 <211> 54  
 <212> PRT  
 <213> Homo sapien

<400> 500

Met Met Thr Ala Ala Leu Leu Trp Trp Asp Tyr Phe Gly Gly Trp Met  
 1                          5                          10                          15

Trp Pro Arg Glu Val Cys Thr Leu Ser Gly Gln Ala Phe Cys Phe Asp  
                           20                          25                          30

His Phe Val Ala Gln His Leu Thr Gln Gly Ala Arg Asp Ser Arg Pro  
           35                          40                          45

Tyr Val Lys Arg Glu Gly  
           50

636

<210> 501  
 <211> 11  
 <212> PRT  
 <213> Homo sapien

<400> 501

Met Val Phe Phe Ile Thr Phe Ile Val Phe Leu  
 1 5 10

<210> 502  
 <211> 126  
 <212> PRT  
 <213> Homo sapien

<400> 502

Met Thr Gly Phe Gly Asn Pro Ile Ala Ser Glu Phe Gln Gly Gly Glu  
 1 5 10 15

Glu Lys Asp Ala Gly Glu Asn Leu Leu Ser Glu Gly Phe Pro Leu Ala  
 20 25 30

Ala Ser Ser Thr Lys Leu Thr His Lys Leu His Val Lys Phe Pro Asn  
 35 40 45

Leu His Leu Gly Glu Gln Ala Leu Ser Leu Gln Arg Ile Gln Arg His  
 50 55 60

Leu Glu Gly Ile Cys Gln Gly Arg His Arg Val Arg Arg Trp Gly Trp  
 65 70 75 80

Gly Phe Leu Asp Ser Ser Gly Pro Leu Gln Pro His Arg Ala Cys Asn  
 85 90 95

Val Ala Asp Ala Ala Gly Glu Leu Val Ser Glu Arg Arg Met His Glu  
 100 105 110

Ser Glu Leu Glu Thr Glu Gly Gln Lys Asp Gln Glu Lys Lys  
 115 120 125

<210> 503  
 <211> 126  
 <212> PRT  
 <213> Homo sapien

<400> 503

Met Thr Gly Phe Gly Asn Pro Ile Ala Ser Glu Phe Gln Gly Gly Glu  
 1 5 10 15

637

Glu Lys Asp Ala Gly Glu Asn Leu Leu Ser Glu Gly Phe Pro Leu Ala  
20 25 30

Ala Ser Ser Thr Lys Leu Thr His Lys Leu His Val Lys Phe Pro Asn  
35 40 45

Leu His Leu Gly Glu Gln Ala Leu Ser Leu Gln Arg Ile Gln Arg His  
50 55 60

Leu Glu Gly Ile Cys Gln Gly Arg His Arg Val Arg Arg Trp Gly Trp  
65 70 75 80

Gly Phe Leu Asp Ser Ser Gly Pro Leu Gln Pro His Arg Ala Cys Asn  
85 90 95

Val Ala Asp Ala Ala Gly Glu Leu Val Ser Glu Arg Arg Met His Glu  
100 105 110

Ser Glu Leu Glu Thr Glu Gly Gln Lys Asp Gln Glu Lys Lys  
115 120 125

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<210> 504
<211> 10
<212> PRT
<213> Homo sapien
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<400> 504

Met Gly Leu Phe Leu Val Glu Lys Val Leu  
1 5 10

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<210> 505
<211> 141
<212> PRT
<213> Homo sapien
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<400> 505

Met Ser Ile Cys Arg Arg Gln Glu Asp Thr Val Trp Leu Ala Trp Ala  
1 5 10 15

Ser Leu Ala Asp Arg Gly Ala Ala Gln Pro Asp His Arg Gly Phe Met  
20 25 30

Ala Gly Thr Pro Asp His Ser Leu Ile Leu Ser Asp Phe Thr His His  
35 40 45

Leu Ala Ser Ala Gln Ser Cys His Cys Ala Phe Pro Asp Met Ser Ala  
50 55 60

638

Ala Gly Thr His Thr Arg Glu Arg Leu Leu Ser Pro Ala Lys Ser Thr  
65 70 75 80

Gly Glu Lys Ala Leu Pro Pro Gly Lys Gln Arg Gln Pro Cys Ser Val  
85 90 95

Thr Thr Asn Leu Tyr Lys Ala Gln Gly Leu Ile Val Asp Phe Leu Gln  
100 105 110

Gln Val Ser Cys Val Arg Pro Gly Pro Leu Pro Ser Ile Leu Asn Ala  
115 120 125

Arg His Leu Asn Ser Pro Ala Cys Gln Ser Gly Ile Pro  
130 135 140

<210> 506

<211> 141

<212> PRT

<213> Homo sapien

<400> 506

Met Ser Ile Cys Arg Arg Gln Glu Asp Thr Val Trp Leu Ala Trp Ala  
1 5 10 15

Ser Leu Ala Asp Arg Gly Ala Ala Gln Pro Asp His Arg Gly Phe Met  
20 25 30

Ala Gly Thr Pro Asp His Ser Leu Ile Leu Ser Asp Phe Thr His His  
35 40 45

Leu Ala Ser Ala Gln Ser Cys His Cys Ala Phe Pro Asp Met Ser Ala  
50 55 60

Ala Gly Thr His Thr Arg Glu Arg Leu Leu Ser Pro Ala Lys Ser Thr  
65 70 75 80

Gly Glu Lys Ala Leu Pro Pro Gly Lys Gln Arg Gln Pro Cys Ser Val  
85 90 95

Thr Thr Asn Leu Tyr Lys Ala Gln Gly Leu Ile Val Asp Phe Leu Gln  
100 105 110

Gln Val Ser Cys Val Arg Pro Gly Pro Leu Pro Ser Ile Leu Asn Ala  
115 120 125

639

Arg His Leu Asn Ser Pro Ala Cys Gln Ser Gly Ile Pro  
 130 135 140

<210> 507  
 <211> 86  
 <212> PRT  
 <213> Homo sapien

<400> 507

Met Tyr Leu Asn Gln Cys Arg Asn Gln Gly Asn Ile Cys Asp Glu Met  
 1 5 10 15

Gln Arg Arg Asn Cys Leu His Leu Gly Cys Arg Cys Met Ala Met Ala  
 20 25 30

Lys Ala Asp Gly Phe Pro Arg Ser Ser Gln Leu Cys Gln Ala Val Glu  
 35 40 45

Ala Thr Val Leu Ala Gly Ala Val Pro Gly Val Gly Ser Lys Ala Pro  
 50 55 60

Pro Ser Asp Gly Leu Ile Glu Thr Arg Leu Gly Tyr Phe Trp Asp Ser  
 65 70 75 80

Ser Leu Pro Ala Pro Leu  
 85

<210> 508  
 <211> 32  
 <212> PRT  
 <213> Homo sapien

<400> 508

Met Lys Tyr Leu Ala Asp Gly Ser Leu Leu Lys Pro Asp Glu Leu Glu  
 1 5 10 15

Ser Ser Asp Phe Asn Cys Leu Trp Val Leu Arg Val Lys Ser Leu Arg  
 20 25 30

<210> 509  
 <211> 33  
 <212> PRT  
 <213> Homo sapien

<400> 509

Met Lys Tyr Leu Ala Asp Gly Ser Leu Leu Lys Pro Asp Glu Leu Glu  
 1 5 10 15

640

Ser Ser Asp Phe Val Cys Leu Phe Ser Asp Arg Val Thr Asn His Ser  
 20 25 30

Gly

<210> 510  
 <211> 42  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 510

Met Val Pro Gln Gln Thr Gly Leu Gly Ile Gly Arg His Thr Ala Met  
 1 5 10 15

Ile Cys His Leu Lys His Leu Trp Ser Asp Ser Val Gly Lys Leu Leu  
 20 25 30

Thr Phe Leu Lys Asn Val Leu Thr Phe Lys  
 35 40

<210> 511  
 <211> 47  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 511

Met His Leu Lys Leu Ser Leu Arg His Gln Gln Leu Leu Trp Ala Lys  
 1 5 10 15

Arg Asn Cys Pro Asp Arg Lys Lys His Phe Trp Val Leu Val Lys His  
 20 25 30

Cys Leu Asn Ile Trp Ile Leu Leu Phe Ser Leu Leu Leu Gln Glu  
 35 40 45

<210> 512  
 <211> 30  
 <212> PRT  
 <213> Homo sapien

&lt;400&gt; 512

Met Lys Lys Ser Phe Cys Thr Tyr Thr Asn Val Glu Tyr Tyr Val Ala  
 1 5 10 15

Val Leu Asn Phe Lys Asn Gln Met Gln Lys Ile Ser Val Tyr  
 20 25 30

641

<210> 513  
 <211> 21  
 <212> PRT  
 <213> Homo sapien

<400> 513

Met Phe Gln Arg Phe Ser Pro Val Phe Ser Ser Lys Ser Leu Met Gly  
 1 5 10 15

Leu Phe Phe Phe Phe  
 20

<210> 514  
 <211> 144  
 <212> PRT  
 <213> Homo sapien

<400> 514

Met Leu Ile Pro Lys Ser Pro Pro Gly Ala Leu Ser Asp His Lys Ser  
 1 5 10 15

Pro Thr Ser Ser Pro Pro Ala Ala Thr Trp Lys Pro Ala Phe Pro Pro  
 20 25 30

Ala Gln His Leu Gln Ala Ser Pro Gly Gln Pro Ala Gln Val His Val  
 35 40 45

Leu Pro Phe Pro Pro Asp Pro Thr Ser Ser Pro Pro Arg Gln Ser Pro  
 50 55 60

Ile Pro Gly Gln Ser Arg Arg Gln Leu Arg Pro Cys Lys Trp Leu Lys  
 65 70 75 80

Asp Pro Val Trp Cys His Gly Leu Asp Trp Ser Arg Ser Gln Thr Val  
 85 90 95

Ile Ser Asn Pro Lys Leu Gly Asn Phe Met Pro Leu Phe Ser Pro Glu  
 100 105 110

Pro Ala Leu Thr Ala Thr Pro Cys Gly Val Leu Gly Pro Trp Pro Phe  
 115 120 125

Thr Leu Ser Gln Glu Gly Pro Cys Cys Arg Pro Trp Pro Ser Gly Ser  
 130 135 140

<210> 515  
 <211> 966  
 <212> PRT



642

&lt;213&gt; Homo sapien

&lt;400&gt; 515

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro

643

225		230		235		240
Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His						
	245		250		255	
Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val						
	260		265		270	
Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg						
	275		280		285	
His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser						
	290		295		300	
Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly						
	305		310		315	320
Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn						
		325		330		335
Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser						
	340		345		350	
Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg						
	355		360		365	
His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg						
	370		375		380	
Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys						
	385		390		395	400
Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg						
		405		410		415
Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala						
	420		425		430	
Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro						
	435		440		445	
Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys						
	450		455		460	
Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu						
	465		470		475	480

644

Phe Gln Ala Glu Asp Arg Asp Asp Met Leu Gly Trp Ile Arg Ala Ile  
 485 490 495

Arg Glu Asn Ser Arg Ala Glu Gly Glu Asp Pro Gly Cys Ala Asn Gln  
 500 505 510

Ala Leu Ile Ser Lys Lys Leu Asn Asp Tyr Arg Lys Val Ser His Ser  
 515 520 525

Ser Gly Pro Lys Ala Asp Ser Ser Pro Lys Gly Ser Arg Gly Leu Gly  
 530 535 540

Gly Leu Lys Ser Glu Phe Leu Lys Gln Ser Ala Ala Arg Gly Leu Arg  
 545 550 555 560

Thr Gln Asp Leu Pro Ala Gly Ser Lys Asp Asp Ser Ala Ala Ala Pro  
 565 570 575

Lys Thr Pro Trp Gly Ile Asn Ile Ile Lys Lys Asn Lys Lys Ala Ala  
 580 585 590

Pro Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu  
 595 600 605

Asn Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu  
 610 615 620

Ala Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn  
 625 630 635 640

Ala Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp  
 645 650 655

Ile Asn Leu Gln Asp Glu Arg Trp Gln Asp Leu Asn Val Ile Ser Ser  
 660 665 670

Leu Leu Lys Ser Phe Phe Arg Lys Leu Pro Glu Pro Leu Phe Thr Asp  
 675 680 685

Asp Lys Tyr Asn Asp Phe Ile Glu Ala Asn Arg Ile Glu Asp Ala Arg  
 690 695 700

Glu Arg Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His  
 705 710 715 720

645

Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala  
                     725                    730                    735

Asp His Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val  
                     740                    745                    750

Phe Gly Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met  
                     755                    760                    765

Val Thr His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln  
                     770                    775                    780

His Ser Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Thr  
                     785                    790                    795                    800

Pro Val Gly Asp Lys Glu Pro Gln Ala Val Pro Asn Ile Glu Tyr Leu  
                     805                    810                    815

Leu Pro Asn Ile Gly Arg Thr Val Pro Pro Gly Asp Pro Gly Ser Ala  
                     820                    825                    830

Asp Leu Leu Glu Ile Val Lys Asp Ser Thr Thr Cys Ser Ser Ala Lys  
                     835                    840                    845

Ser Lys Gly Ser Trp Ala Pro Lys Lys Glu Pro Tyr Ala Arg Glu Met  
                     850                    855                    860

Leu Ala Ile Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys Arg  
                     865                    870                    875                    880

Arg Glu Ala Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu Gln  
                     885                    890                    895

Glu Ala His Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln Glu  
                     900                    905                    910

Arg Pro Pro Gly Ser Arg Gly Pro Ala Ala Ala Ala Asp Ala Pro Arg  
                     915                    920                    925

Arg Arg His Arg Gly Pro Arg Thr Arg Gln Ser Pro Gly Gly Ala Gly  
                     930                    935                    940

Gly Ala Ala Gly Arg Gly Asp Ala Leu His Cys Val Gly Leu Ile Gln  
                     945                    950                    955                    960

646

Pro Val Thr Met Asp Arg  
965

<210> 516  
<211> 202  
<212> PRT  
<213> Homo sapien

<400> 516

Asp Leu Pro Gly Pro Phe Tyr Glu Arg Ser Asn Ser Leu Trp Asp Pro  
1 5 10 15

Phe Ser Asp Leu Arg Leu Pro Phe Ile Ser Ser Cys Gly Ala Ala Ala  
20 25 30

Thr Leu Ser Arg Ser Phe Ser Ser Pro Lys Asn Lys Lys Ala Ala Pro  
35 40 45

Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu Asn  
50 55 60

Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu Ala  
65 70 75 80

Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn Ala  
85 90 95

Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp Ile  
100 105 110

Asn Leu Gln Asp Glu Arg Trp Gln Asp Leu Asn Val Ile Ser Ser Leu  
115 120 125

Leu Lys Ser Phe Phe Arg Lys Leu Pro Glu Pro Leu Phe Thr Asp Asp  
130 135 140

Lys Tyr Asn Asp Phe Ile Glu Ala Asn Arg Ile Glu Asp Ala Arg Glu  
145 150 155 160

Arg Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His Tyr  
165 170 175

Tyr Glu Thr Leu Lys Phe Leu Val Gly Pro Phe Leu Arg Gln Arg Leu  
180 185 190

Pro Phe Ile Ser Ser Cys Gly Asp Ala Ala  
195 200

647

<210> 517  
 <211> 103  
 <212> PRT  
 <213> Homo sapien

<400> 517

Met Leu Ala Ile Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys  
 1 5 10 15

Arg Arg Glu Ala Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu  
 20 25 30

Gln Glu Ala His Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln  
 35 40 45

Glu Arg Pro Pro Gly Ser Arg Gly Pro Ala Ala Ala Ala Asp Ala Pro  
 50 55 60

Arg Arg Arg His Arg Gly Pro Arg Thr Arg Gln Ser Pro Gly Gly Ala  
 65 70 75 80

Gly Gly Ala Ala Gly Arg Gly Asp Ala Leu His Cys Val Gly Leu Ile  
 85 90 95

Gln Pro Val Thr Met Asp Arg  
 100

<210> 518  
 <211> 958  
 <212> PRT  
 <213> Homo sapien

<400> 518

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala

648

65

70

75

80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
85 90 95

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
115 120 125

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
130 135 140

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
210 215 220

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
225 230 235 240

Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His  
245 250 255

Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val  
260 265 270

Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg  
275 280 285

His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser  
290 295 300

Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly  
305 310 315 320

649

Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn  
 325 330 335

Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser  
 340 345 350

Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg  
 355 360 365

His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg  
 370 375 380

Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys  
 385 390 395 400

Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg  
 405 410 415

Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala  
 420 425 430

Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro  
 435 440 445

Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys  
 450 455 460

Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu  
 465 470 475 480

Phe Gln Ala Glu Asp Arg Asp Asp Met Leu Gly Trp Ile Arg Ala Ile  
 485 490 495

Arg Glu Asn Ser Arg Ala Glu Gly Glu Asp Pro Gly Cys Ala Asn Gln  
 500 505 510

Ala Leu Ile Ser Lys Lys Leu Asn Asp Tyr Arg Lys Val Ser His Ser  
 515 520 525

Ser Gly Pro Lys Ala Asp Ser Ser Pro Lys Gly Ser Arg Gly Leu Gly  
 530 535 540

Gly Leu Lys Ser Glu Phe Leu Lys Gln Ser Ala Ala Arg Gly Leu Arg  
 545 550 555 560



650

Thr Gln Asp Leu Pro Ala Gly Ser Lys Asp Asp Ser Ala Ala Ala Pro  
 565 570 575

Lys Thr Pro Trp Gly Ile Asn Ile Ile Lys Lys Asn Lys Lys Ala Ala  
 580 585 590

Pro Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu  
 595 600 605

Asn Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu  
 610 615 620

Ala Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn  
 625 630 635 640

Ala Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp  
 645 650 655

Ile Asn Leu Gln Asp Glu Arg Trp Gln Asp Leu Asn Val Ile Ser Ser  
 660 665 670

Leu Leu Lys Ser Phe Phe Arg Lys Leu Pro Glu Pro Leu Phe Thr Asp  
 675 680 685

Asp Lys Tyr Asn Asp Phe Ile Glu Ala Asn Arg Ile Glu Asp Ala Arg  
 690 695 700

Glu Arg Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His  
 705 710 715 720

Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala  
 725 730 735

Asp His Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val  
 740 745 750

Phe Gly Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met  
 755 760 765

Val Thr His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln  
 770 775 780

His Ser Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Thr  
 785 790 795 800

651

Pro Val Gly Asp Lys Glu Pro Gln Ala Val Pro Asn Ile Glu Tyr Leu  
805 810 815

Leu Pro Asn Ile Gly Arg Thr Val Pro Pro Gly Asp Pro Gly Ser Asp  
820 825 830

Ser Thr Thr Cys Ser Ser Ala Lys Ser Lys Gly Ser Trp Ala Pro Lys  
835 840 845

Lys Glu Pro Tyr Ala Arg Glu Met Leu Ala Ile Ser Phe Ile Ser Ala  
850 855 860

Val	Asn	Arg	Lys	Arg	Lys	Lys	Arg	Arg	Glu	Ala	Arg	Gly	Leu	Gly	Ser
865					870					875					880

Ser Thr Asp Asp Asp Ser Glu Gln Glu Ala His Lys Pro Gly Ala Gly  
885 890 895

Ala Thr Ala Pro Gly Thr Gln Glu Arg Pro Pro Gly Ser Arg Gly Pro  
900 905 910

Ala Ala Ala Ala Asp Ala Pro Arg Arg Arg His Arg Gly Pro Arg Thr  
915 920 925

Arg Gln Ser Pro Gly Gly Ala Gly Gly Ala Ala Gly Arg Gly Asp Ala  
930 935 940

Leu His Cys Val Gly Leu Ile Gln Pro Val Thr Met Asp Arg  
945 950 955

<210> 519

<211> 837

<212> PRT

<213> Homo sapien

<400> 519

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
50 55 60

652

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
 225 230 235 240

Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His  
 245 250 255

Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val  
 260 265 270

Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg  
 275 280 285

His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser  
 290 295 300

653

Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly  
305 310 315 320

Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn  
325 330 335

Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser  
340 345 350

Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg  
355 360 365

His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg  
370 375 380

Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys  
385 390 395 400

Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg  
405 410 415

Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala  
420 425 430

Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro  
435 440 445

Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys  
450 455 460

Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu  
465 470 475 480

Phe Gln Ala Glu Asp Arg Asp Asp Met Leu Gly Trp Ile Arg Ala Ile  
485 490 495

Arg Glu Asn Ser Arg Ala Glu Gly Glu Asp Pro Gly Cys Ala Asn Gln  
500 505 510

Ala Leu Ile Ser Lys Lys Leu Asn Asp Tyr Arg Lys Val Ser His Ser  
515 520 525

Ser Gly Pro Lys Ala Asp Ser Ser Pro Lys Gly Ser Arg Gly Leu Gly  
530 535 540

654

Gly Leu Lys Ser Glu Phe Leu Lys Gln Ser Ala Ala Arg Gly Leu Arg  
 545 550 555 560

Thr Gln Asp Leu Pro Ala Gly Ser Lys Asp Asp Ser Ala Ala Ala Pro  
 565 570 575

Lys Thr Pro Trp Gly Ile Asn Ile Ile Lys Lys Asn Lys Lys Ala Ala  
 580 585 590

Pro Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu  
 595 600 605

Asn Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu  
 610 615 620

Ala Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn  
 625 630 635 640

Ala Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp  
 645 650 655

Ile Asn Leu Gln Asp Glu Arg Trp Gln Asp Leu Asn Val Ile Ser Ser  
 660 665 670

Leu Leu Lys Ser Phe Phe Arg Lys Leu Pro Glu Pro Leu Phe Thr Asp  
 675 680 685

Asp Lys Tyr Asn Asp Phe Ile Glu Ala Asn Arg Ile Glu Asp Ala Arg  
 690 695 700

Glu Arg Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His  
 705 710 715 720

Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala  
 725 730 735

Asp His Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val  
 740 745 750

Phe Gly Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met  
 755 760 765

Val Thr His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln  
 770 775 780

His Ser Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Thr

785	790	795	800
Pro Val Gly Asp Lys Glu Pro Gln Ala Val Pro Asn Ile Glu Tyr Leu	805	810	815
Leu Pro Asn Ile Gly Arg Thr Val Pro Pro Gly Asp Pro Gly Ser Ala	820	825	830
Asp Leu Leu Glu Ile	835		
<210> 520			
<211> 470			
<212> PRT			
<213> Homo sapien			
<400> 520			
Met Leu Gly Trp Ile Arg Ala Ile Arg Glu Asn Ser Arg Ala Glu Gly	5	10	15
1			
Glu Asp Pro Gly Cys Ala Asn Gln Ala Leu Ile Ser Lys Lys Leu Asn	20	25	30
Asp Tyr Arg Lys Val Ser His Ser Ser Gly Pro Lys Ala Asp Ser Ser	35	40	45
Pro Lys Gly Ser Arg Gly Leu Gly Gly Leu Lys Ser Glu Phe Leu Lys	50	55	60
Gln Ser Ala Ala Arg Gly Leu Arg Thr Gln Asp Leu Pro Ala Gly Ser	65	70	75
Lys Asp Asp Ser Ala Ala Ala Pro Lys Thr Pro Trp Gly Ile Asn Ile	85	90	95
Ile Lys Lys Asn Lys Lys Ala Ala Pro Arg Ala Phe Gly Val Arg Leu	100	105	110
Glu Glu Cys Gln Pro Ala Thr Glu Asn Gln Arg Val Pro Leu Ile Val	115	120	125
Ala Ala Cys Cys Arg Ile Val Glu Ala Arg Gly Leu Glu Ser Thr Gly	130	135	140
Ile Tyr Arg Val Pro Gly Asn Asn Ala Val Val Ser Ser Leu Gln Glu	145	150	155
			160

656

Gln Leu Asn Arg Gly Pro Gly Asp Ile Asn Leu Gln Asp Glu Arg Trp  
                                   165                                  170                                  175

Gln Asp Leu Asn Val Ile Ser Ser Leu Leu Lys Ser Phe Phe Arg Lys  
                                   180                                  185                                  190

Leu Pro Glu Pro Leu Phe Thr Asp Asp Lys Tyr Asn Asp Phe Ile Glu  
                                   195                                  200                                  205

Ala Asn Arg Ile Glu Asp Ala Arg Glu Arg Met Arg Thr Leu Arg Lys  
                                   210                                  215                                  220

Leu Ile Arg Asp Leu Pro Gly His Tyr Tyr Glu Thr Leu Lys Phe Leu  
                                   225                                  230                                  235                                  240

Val Gly His Leu Lys Thr Ile Ala Asp His Ser Glu Lys Asn Lys Met  
                                   245                                  250                                  255

Glu Pro Arg Asn Leu Ala Leu Val Phe Gly Pro Thr Leu Val Arg Thr  
                                   260                                  265                                  270

Ser Glu Asp Asn Met Thr Asp Met Val Thr His Met Pro Asp Arg Tyr  
                                   275                                  280                                  285

Lys Ile Val Glu Thr Leu Ile Gln His Ser Asp Trp Phe Phe Ser Asp  
                                   290                                  295                                  300

Glu Glu Asp Lys Gly Glu Arg Thr Pro Val Gly Asp Lys Glu Pro Gln  
                                   305                                  310                                  315                                  320

Ala Val Pro Asn Ile Glu Tyr Leu Leu Pro Asn Ile Gly Arg Thr Val  
                                   325                                  330                                  335

Pro Pro Gly Asp Pro Gly Ser Asp Ser Thr Thr Cys Ser Ser Ala Lys  
                                   340                                  345                                  350

Ser Lys Gly Ser Trp Ala Pro Lys Lys Glu Pro Tyr Ala Arg Glu Met  
                                   355                                  360                                  365

Leu Ala Ile Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys Arg  
                                   370                                  375                                  380

Arg Glu Ala Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu Gln  
                                   385                                  390                                  395                                  400

657

Glu Ala His Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln Glu  
 405 410 415

Arg Pro Pro Gly Ser Arg Gly Pro Ala Ala Ala Ala Asp Ala Pro Arg  
 420 425 430

Arg Arg His Arg Gly Pro Arg Thr Arg Gln Ser Pro Gly Gly Ala Gly  
 435 440 445

Gly Ala Ala Gly Arg Gly Asp Ala Leu His Cys Val Gly Leu Ile Gln  
 450 455 460

Pro Val Thr Met Asp Arg  
 465 470

<210> 521  
 <211> 252  
 <212> PRT  
 <213> Homo sapien

<400> 521

Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His Tyr Tyr  
 1 5 10 15

Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala Asp His  
 20 25 30

Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val Phe Gly  
 35 40 45

Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met Val Thr  
 50 55 60

His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln His Ser  
 65 70 75 80

Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Thr Pro Val  
 85 90 95

Gly Asp Lys Glu Pro Gln Ala Val Pro Asn Ile Glu Tyr Leu Leu Pro  
 100 105 110

Asn Ile Gly Arg Thr Val Pro Pro Gly Asp Pro Gly Ser Asp Ser Thr  
 115 120 125

Thr Cys Ser Ser Ala Lys Ser Lys Gly Ser Trp Ala Pro Lys Lys Glu  
 130 135 140



658

Pro Tyr Ala Arg Glu Met Leu Ala Ile Ser Phe Ile Ser Ala Val Asn  
 145 150 155 160

Arg Lys Arg Lys Lys Arg Arg Glu Ala Arg Gly Leu Gly Ser Ser Thr  
 165 170 175

Asp Asp Asp Ser Glu Gln Glu Ala His Lys Pro Gly Ala Gly Ala Thr  
 180 185 190

Ala Pro Gly Thr Gln Glu Arg Pro Pro Gly Ser Arg Gly Pro Ala Ala  
 195 200 205

Ala Ala Asp Ala Pro Arg Arg Arg His Arg Gly Pro Arg Thr Arg Gln  
 210 215 220

Ser Pro Gly Gly Ala Gly Gly Ala Ala Gly Arg Gly Asp Ala Leu His  
 225 230 235 240

Cys Val Gly Leu Ile Gln Pro Val Thr Met Asp Arg  
 245 250

<210> 522  
 <211> 693  
 <212> PRT  
 <213> Homo sapien

<400> 522

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

659

Thr	Pro	Ser	Gly	Leu	Gln	Gly	Leu	Asp	Asp	Leu	Gly	Tyr	Ile	Gly	Tyr
			100					105					110		
Arg	Ser	Tyr	Ser	Pro	Ser	Phe	Gln	Arg	Arg	Thr	Gly	Leu	Leu	His	Ala
		115					120					125			
Leu	Ser	Phe	Arg	Asp	Ser	Pro	Phe	Gly	Gly	Leu	Pro	Thr	Phe	Asn	Leu
	130					135					140				
Ala	Gln	Ser	Pro	Ala	Ser	Phe	Pro	Pro	Glu	Ala	Ser	Glu	Pro	Pro	Arg
145					150					155					160
Val	Val	Arg	Pro	Glu	Pro	Ser	Thr	Arg	Ala	Leu	Glu	Pro	Pro	Ala	Glu
				165					170					175	
Asp	Arg	Gly	Asp	Glu	Val	Val	Leu	Arg	Gln	Lys	Pro	Pro	Thr	Gly	Arg
			180					185						190	
Lys	Val	Gln	Leu	Thr	Pro	Ala	Arg	Gln	Met	Asn	Leu	Gly	Phe	Gly	Asp
		195					200					205			
Glu	Ser	Pro	Glu	Pro	Glu	Ala	Ser	Gly	Arg	Gly	Glu	Arg	Leu	Gly	Arg
	210					215					220				
Lys	Val	Ala	Pro	Leu	Ala	Thr	Thr	Glu	Asp	Ser	Leu	Ala	Ser	Ile	Pro
225					230					235					240
Phe	Ile	Asp	Glu	Pro	Thr	Ser	Pro	Ser	Ile	Asp	Leu	Gln	Ala	Lys	His
				245					250					255	
Val	Pro	Ala	Ser	Ala	Val	Val	Ser	Ser	Ala	Met	Asn	Ser	Ala	Pro	Val
			260					265					270		
Leu	Gly	Thr	Ser	Pro	Ser	Ser	Pro	Thr	Phe	Thr	Phe	Thr	Leu	Gly	Arg
		275					280					285			
His	Tyr	Ser	Gln	Asp	Cys	Ser	Ser	Ile	Lys	Ala	Gly	Arg	Arg	Ser	Ser
	290					295					300				
Tyr	Leu	Leu	Ala	Ile	Thr	Thr	Glu	Arg	Ser	Lys	Ser	Cys	Asp	Asp	Gly
305					310					315					320
Leu	Asn	Thr	Phe	Arg	Asp	Glu	Gly	Arg	Val	Leu	Arg	Arg	Leu	Pro	Asn
				325					330					335	
Arg	Ile	Pro	Ser	Leu	Arg	Met	Leu	Arg	Ser	Phe	Phe	Thr	Asp	Gly	Ser

660

340	345	350
Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg		
355	360	365
His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg		
370	375	380
Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys		
385	390	395 400
Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg		
405	410	415
Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala		
420	425	430
Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro		
435	440	445
Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys		
450	455	460
Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu		
465	470	475 480
Phe Gln Ala Glu Asp Arg Asp Asp Met Leu Gly Trp Ile Arg Ala Ile		
485	490	495
Arg Glu Asn Ser Arg Ala Glu Gly Glu Asp Pro Gly Cys Ala Asn Gln		
500	505	510
Ala Leu Ile Ser Lys Lys Leu Asn Asp Tyr Arg Lys Val Ser His Ser		
515	520	525
Ser Gly Pro Lys Ala Asp Ser Ser Pro Lys Gly Ser Arg Gly Leu Gly		
530	535	540
Gly Leu Lys Ser Glu Phe Leu Lys Gln Ser Ala Ala Arg Gly Leu Arg		
545	550	555 560
Thr Gln Asp Leu Pro Ala Gly Ser Lys Asp Asp Ser Ala Ala Ala Pro		
565	570	575
Lys Thr Pro Trp Gly Ile Asn Ile Ile Lys Lys Asn Lys Lys Ala Ala		
580	585	590

661

Pro Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu  
 595 600 605

Asn Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu  
 610 615 620

Ala Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn  
 625 630 635 640

Ala Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp  
 645 650 655

Ile Asn Leu Gln Asp Glu Arg Trp Gln Asp Leu Asn Val Ile Ser Ser  
 660 665 670

Leu Leu Lys Ser Phe Phe Arg Lys Leu Pro Glu Pro Leu Phe Thr Asp  
 675 680 685

Gly Ala Leu Leu Phe  
 690

<210> 523  
 <211> 697  
 <212> PRT  
 <213> Homo sapien

<400> 523

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

662

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
 225 230 235 240

Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His  
 245 250 255

Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val  
 260 265 270

Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg  
 275 280 285

His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser  
 290 295 300

Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly  
 305 310 315 320

Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn  
 325 330 335

Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser

663

340	345	350
Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg		
355	360	365
His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg		
370	375	380
Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys		
385	390	400
Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg		
405	410	415
Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala		
420	425	430
Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro		
435	440	445
Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys		
450	455	460
Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu		
465	470	475
Phe Gln Ala Glu Asp Arg Asp Asp Met Leu Gly Trp Ile Arg Ala Ile		
485	490	495
Arg Glu Asn Ser Arg Ala Glu Gly Glu Asp Pro Gly Cys Ala Asn Gln		
500	505	510
Ala Leu Ile Ser Lys Lys Leu Asn Asp Tyr Arg Lys Val Ser His Ser		
515	520	525
Ser Gly Pro Lys Ala Asp Ser Ser Pro Lys Gly Ser Arg Gly Leu Gly		
530	535	540
Gly Leu Lys Ser Glu Phe Leu Lys Gln Ser Ala Ala Arg Gly Leu Arg		
545	550	555
Thr Gln Asp Leu Pro Ala Gly Ser Lys Asp Asp Ser Ala Ala Ala Pro		
565	570	575
Lys Thr Pro Trp Gly Ile Asn Ile Ile Lys Lys Asn Lys Lys Ala Ala		
580	585	590

664

Pro Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu  
 595 600 605

Asn Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu  
 610 615 620

Ala Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn  
 625 630 635 640

Ala Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp  
 645 650 655

Ile Asn Leu Gln Asp Glu Val Gly Glu Ala Gly Gly Ser Val Glu Gly  
 660 665 670

Gly Leu Arg Trp Cys Val Gly Gly Ala Pro Leu Gly Glu Phe Cys Gly  
 675 680 685

Leu Leu Cys Cys Met His Cys Ala Leu  
 690 695

<210> 524

<211> 252

<212> PRT

<213> Homo sapien

<400> 524

Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His Tyr Tyr  
 1 5 10 15

Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala Asp His  
 20 25 30

Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val Phe Gly  
 35 40 45

Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met Val Thr  
 50 55 60

His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln His Ser  
 65 70 75 80

Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Thr Pro Val  
 85 90 95

665

Gly Asp Lys Glu Pro Gln Ala Val Pro Asn Ile Glu Tyr Leu Leu Pro  
 100 105 110

Asn Ile Gly Arg Thr Val Pro Pro Gly Asp Pro Gly Ser Asp Ser Thr  
 115 120 125

Thr Cys Ser Ser Ala Lys Ser Lys Gly Ser Trp Ala Pro Lys Lys Glu  
 130 135 140

Pro Tyr Ala Arg Glu Met Leu Ala Ile Ser Phe Ile Ser Ala Val Asn  
 145 150 155 160

Arg Lys Arg Lys Lys Arg Arg Glu Ala Arg Gly Leu Gly Ser Ser Thr  
 165 170 175

Asp Asp Asp Ser Glu Gln Glu Ala His Lys Pro Gly Ala Gly Ala Thr  
 180 185 190

Ala Pro Gly Thr Gln Glu Arg Pro Pro Gly Ser Arg Gly Pro Ala Ala  
 195 200 205

Ala Ala Asp Ala Pro Arg Arg Arg His Arg Gly Pro Arg Thr Arg Gln  
 210 215 220

Ser Pro Gly Gly Ala Gly Gly Ala Ala Gly Arg Gly Asp Ala Leu His  
 225 230 235 240

Cys Val Gly Leu Ile Gln Pro Val Thr Met Asp Arg  
 245 250

<210> 525

<211> 568

<212> PRT

<213> Homo sapien

<400> 525

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60



666

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
 225 230 235 240

Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His  
 245 250 255

Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val  
 260 265 270

Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg  
 275 280 285

His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser  
 290 295 300

667

Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly  
 305 310 315 320

Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn  
 325 330 335

Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser  
 340 345 350

Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg  
 355 360 365

His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg  
 370 375 380

Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys  
 385 390 395 400

Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg  
 405 410 415

Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala  
 420 425 430

Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro  
 435 440 445

Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys  
 450 455 460

Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu  
 465 470 475 480

Phe Gln Ala Glu Asp Arg Asp Asp Met Leu Gly Trp Ile Arg Ala Ile  
 485 490 495

Arg Glu Asn Ser Arg Ala Glu Gly Glu Val Arg Ala Arg Pro Ala Arg  
 500 505 510

Gln Pro Gln Arg Ala Gly Gly Val Ala Ser His Arg Leu Trp Thr Trp  
 515 520 525

Asp Ala Arg Ser Glu Pro His Phe Pro Leu Leu Glu Arg Gly Ala Asp  
 530 535 540

668

Arg Ser Ala Pro Arg Asp Cys Val Pro Gln Gly Phe Gly Val Arg Arg  
 545 550 555 560

Val His Arg Gln Gly Ser Arg Gly  
 565

<210> 526  
 <211> 260  
 <212> PRT  
 <213> Homo sapien

<400> 526

Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His Tyr Tyr  
 1 5 10 15

Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala Asp His  
 20 25 30

Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val Phe Gly  
 35 40 45

Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met Val Thr  
 50 55 60

His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln His Ser  
 65 70 75 80

Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Thr Pro Val  
 85 90 95

Gly Asp Lys Glu Pro Gln Ala Val Pro Asn Ile Glu Tyr Leu Leu Pro  
 100 105 110

Asn Ile Gly Arg Thr Val Pro Pro Gly Asp Pro Gly Ser Ala Asp Leu  
 115 120 125

Leu Glu Asp Leu Lys Asp Ser Thr Thr Cys Ser Ser Ala Lys Ser Lys  
 130 135 140

Gly Ser Trp Ala Pro Lys Lys Glu Pro Tyr Ala Arg Glu Met Leu Ala  
 145 150 155 160

Ile Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys Arg Arg Glu  
 165 170 175

Ala Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu Gln Glu Ala  
 180 185 190

669

His Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln Glu Arg Pro  
 195 200 205

Pro Gly Ser Arg Gly Pro Ala Ala Ala Ala Asp Ala Pro Arg Arg Arg  
 210 215 220

His Arg Gly Pro Arg Thr Arg Gln Ser Pro Gly Gly Ala Gly Gly Ala  
 225 230 235 240

Ala Gly Arg Gly Asp Ala Leu His Cys Val Gly Leu Ile Gln Pro Val  
 245 250 255

Thr Met Asp Arg  
 260

<210> 527  
 <211> 125  
 <212> PRT  
 <213> Homo sapien

<400> 527

Met Leu Gly Trp Ile Arg Ala Ile Arg Glu Asn Ser Arg Ala Glu Gly  
 1 5 10 15

Glu Asp Pro Gly Cys Ala Asn Gln Ala Leu Ile Ser Lys Lys Leu Asn  
 20 25 30

Asp Tyr Arg Lys Val Ser His Ser Ser Gly Pro Lys Ala Asp Ser Ser  
 35 40 45

Pro Lys Gly Ser Arg Gly Leu Gly Gly Leu Lys Ser Glu Phe Leu Lys  
 50 55 60

Gln Ser Ala Ala Arg Gly Leu Arg Thr Gln Asp Leu Pro Ala Gly Ser  
 65 70 75 80

Lys Asp Asp Ser Ala Ala Ala Pro Lys Thr Pro Trp Gly Ile Asn Ile  
 85 90 95

Ile Lys Lys Asn Lys Lys Ala Ala Pro Arg Ala Phe Gly Val Arg Leu  
 100 105 110

Glu Glu Cys Gln Pro Ala Thr Glu Asn Gln Arg Val Pro  
 115 120 125

670

<210> 528  
 <211> 225  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> MISC\_FEATURE  
 <222> (132)..(132)  
 <223> x= any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (140)..(140)  
 <223> x= any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (153)..(153)  
 <223> x= any amino acid

<400> 528

Asp Leu Pro Gly Pro Phe Tyr Glu Arg Ser Asn Ser Leu Trp Asp Pro  
 1 5 10 15

Phe Ser Asp Leu Arg Leu Pro Phe Ile Ser Ser Cys Gly Ala Ala Ala  
 20 25 30

Thr Leu Ser Arg Ser Phe Ser Ser Pro Lys Asn Lys Lys Ala Ala Pro  
 35 40 45

Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu Asn  
 50 55 60

Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu Ala  
 65 70 75 80

Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn Ala  
 85 90 95

Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp Ile  
 100 105 110

Asn Leu Gln Asp Glu Arg His Ser Ala Thr Glu Arg Val Ile Leu Leu  
 115 120 125

Glu Ser Arg Xaa Ala Leu Leu Tyr Asn Gly Ala Xaa Ser Leu Arg Cys  
 130 135 140

671

Lys Cys Arg Ser Thr His Glu Ser Xaa Ser Leu Tyr Gln Ala Val Asp  
 145 150 155 160

Asp Leu Arg Leu Ile Thr Glu His Ser Ile Asp Gly Pro Ser Pro His  
 165 170 175

Ser Asp Gly Leu Arg Val Glu Gln Asn Glu Glu Leu Arg Lys Leu Ile  
 180 185 190

Arg Asp Leu Pro Gly His Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly  
 195 200 205

Pro Phe Leu Arg Gln Arg Leu Pro Phe Ile Ser Ser Cys Gly Ala Ala  
 210 215 220

Ala  
 225

<210> 529  
 <211> 917  
 <212> PRT  
 <213> Homo sapien

<400> 529

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125

672

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
 225 230 235 240

Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His  
 245 250 255

Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val  
 260 265 270

Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg  
 275 280 285

His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser  
 290 295 300

Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly  
 305 310 315 320

Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn  
 325 330 335

Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser  
 340 345 350

Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg  
 355 360 365

673

His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg  
 370 375 380

Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys  
 385 390 395 400

Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg  
 405 410 415

Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala  
 420 425 430

Ala Ala Gly Ala Ala Gly Pro Ala Gln Ala Glu Asp Arg Asp Asp Met  
 435 440 445

Leu Gly Trp Ile Arg Ala Ile Arg Glu Asn Ser Arg Ala Glu Gly Glu  
 450 455 460

Asp Pro Gly Cys Ala Asn Gln Ala Leu Ile Ser Lys Lys Leu Asn Asp  
 465 470 475 480

Tyr Arg Lys Val Ser His Ser Ser Gly Pro Lys Ala Asp Ser Ser Pro  
 485 490 495

Lys Gly Ser Arg Gly Leu Gly Gly Leu Lys Ser Glu Phe Leu Lys Gln  
 500 505 510

Ser Ala Ala Arg Gly Leu Arg Thr Gln Asp Leu Pro Ala Gly Ser Lys  
 515 520 525

Asp Asp Ser Ala Ala Ala Pro Lys Thr Pro Trp Gly Ile Asn Ile Ile  
 530 535 540

Lys Lys Asn Lys Lys Ala Ala Pro Arg Ala Phe Gly Val Arg Leu Glu  
 545 550 555 560

Glu Cys Gln Pro Ala Thr Glu Asn Gln Arg Val Pro Leu Ile Val Ala  
 565 570 575

Ala Cys Cys Arg Ile Val Glu Ala Arg Gly Leu Glu Ser Thr Gly Ile  
 580 585 590

Tyr Arg Val Pro Gly Asn Asn Ala Val Val Ser Ser Leu Gln Glu Gln  
 595 600 605



674

Leu Asn Arg Gly Pro Gly Asp Ile Asn Leu Gln Asp Glu Arg Trp Gln  
 610 615 620

Asp Leu Asn Val Ile Ser Ser Leu Leu Lys Ser Phe Phe Arg Lys Leu  
 625 630 635 640

Pro Glu Pro Leu Phe Thr Asp Asp Lys Tyr Asn Asp Phe Ile Glu Ala  
 645 650 655

Asn Arg Ile Glu Asp Ala Arg Glu Arg Met Arg Thr Leu Arg Lys Leu  
 660 665 670

Ile Arg Asp Leu Pro Gly His Tyr Tyr Glu Thr Leu Lys Phe Leu Val  
 675 680 685

Gly His Leu Lys Thr Ile Ala Asp His Ser Glu Lys Asn Lys Met Glu  
 690 695 700

Pro Arg Asn Leu Ala Leu Val Phe Gly Pro Thr Leu Val Arg Thr Ser  
 705 710 715 720

Glu Asp Asn Met Thr Asp Met Val Thr His Met Pro Asp Arg Tyr Lys  
 725 730 735

Ile Val Glu Thr Leu Ile Gln His Ser Asp Trp Phe Phe Ser Asp Glu  
 740 745 750

Glu Asp Lys Gly Glu Arg Thr Pro Val Gly Asp Lys Glu Pro Gln Ala  
 755 760 765

Val Pro Asn Ile Glu Tyr Leu Leu Pro Asn Ile Gly Arg Thr Val Pro  
 770 775 780

Pro Gly Asp Pro Gly Ser Asp Ser Thr Thr Cys Ser Ser Ala Lys Ser  
 785 790 795 800

Lys Gly Ser Trp Ala Pro Lys Lys Glu Pro Tyr Ala Arg Glu Met Leu  
 805 810 815

Ala Ile Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys Arg Arg  
 820 825 830

Glu Ala Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu Gln Glu  
 835 840 845

Ala His Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln Glu Arg

675

850

855

860

Pro Pro Gly Ser Arg Gly Pro Ala Ala Ala Ala Asp Ala Pro Arg Arg  
 865 870 875 880

Arg His Arg Gly Pro Arg Thr Arg Gln Ser Pro Gly Gly Ala Gly Gly  
 885 890 895

Ala Ala Gly Arg Gly Asp Ala Leu His Cys Val Gly Leu Ile Gln Pro  
 900 905 910

Val Thr Met Asp Arg  
 915

<210> 530  
 <211> 851  
 <212> PRT  
 <213> Homo sapien

<400> 530

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140

676

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
 225 230 235 240

Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His  
 245 250 255

Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val  
 260 265 270

Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg  
 275 280 285

His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser  
 290 295 300

Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly  
 305 310 315 320

Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn  
 325 330 335

Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser  
 340 345 350

Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg  
 355 360 365

His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg  
 370 375 380

677

Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys  
 385 390 395 400

Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg  
 405 410 415

Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala  
 420 425 430

Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro  
 435 440 445

Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys  
 450 455 460

Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu  
 465 470 475 480

Phe Gln Ala Glu Asp Arg Asp Asp Met Leu Gly Trp Ile Arg Ala Ile  
 485 490 495

Arg Glu Asn Ser Arg Ala Glu Gly Glu Asp Pro Gly Cys Ala Asn Gln  
 500 505 510

Ala Leu Ile Ser Lys Lys Leu Asn Asp Tyr Arg Lys Val Ser His Ser  
 515 520 525

Ser Gly Pro Lys Ala Asp Ser Ser Pro Lys Gly Ser Arg Gly Leu Gly  
 530 535 540

Gly Leu Lys Ser Glu Phe Leu Lys Gln Ser Ala Ala Arg Gly Leu Arg  
 545 550 555 560

Thr Gln Asp Leu Pro Ala Gly Ser Lys Asp Asp Ser Ala Ala Ala Pro  
 565 570 575

Lys Thr Pro Trp Gly Ile Asn Ile Ile Lys Lys Asn Lys Lys Ala Ala  
 580 585 590

Pro Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu  
 595 600 605

Asn Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu  
 610 615 620

Ala Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn

678

625		630		635		640
Ala Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp						
	645			650		655
Ile Asn Leu Gln Asp Glu Arg Trp Gln Asp Leu Asn Val Ile Ser Ser						
	660			665		670
Leu Leu Lys Ser Phe Phe Arg Lys Leu Pro Glu Pro Leu Phe Thr Asp						
	675			680		685
Asp Lys Tyr Asn Asp Phe Ile Glu Ala Asn Arg Ile Glu Asp Ala Arg						
	690			695		700
Glu Arg Met Arg Thr Leu Arg Lys Leu Ile Arg Asp Leu Pro Gly His						
705		710		715		720
Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala						
	725			730		735
Asp His Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val						
	740			745		750
Phe Gly Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met						
	755			760		765
Val Thr His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln						
	770			775		780
His Ser Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Thr						
785		790		795		800
Pro Val Gly Asp Lys Glu Pro Gln Ala Val Pro Asn Ile Glu Tyr Leu						
	805			810		815
Leu Pro Asn Ile Gly Arg Thr Val Pro Pro Gly Asp Pro Gly Ser Asp						
	820			825		830
Ser Thr Thr Cys Ser Ser Ala Lys Ser Lys Val Arg Met Lys Ala Ile						
	835			840		845
Leu Lys Ala						
	850					

&lt;210&gt; 531

&lt;211&gt; 926

679

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 531

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15

Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30

Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45

Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60

Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80

Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95

Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110

Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125

Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140

Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160

Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175

Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190

Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205

Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220

680

Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
 225 230 235 240

Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His  
 245 250 255

Val Pro Ala Ser Ala Val Val Ser Ser Ala Met Asn Ser Ala Pro Val  
 260 265 270

Leu Gly Thr Ser Pro Ser Ser Pro Thr Phe Thr Phe Thr Leu Gly Arg  
 275 280 285

His Tyr Ser Gln Asp Cys Ser Ser Ile Lys Ala Gly Arg Arg Ser Ser  
 290 295 300

Tyr Leu Leu Ala Ile Thr Thr Glu Arg Ser Lys Ser Cys Asp Asp Gly  
 305 310 315 320

Leu Asn Thr Phe Arg Asp Glu Gly Arg Val Leu Arg Arg Leu Pro Asn  
 325 330 335

Arg Ile Pro Ser Leu Arg Met Leu Arg Ser Phe Phe Thr Asp Gly Ser  
 340 345 350

Leu Asp Ser Trp Gly Thr Ser Glu Asp Ala Asp Ala Pro Ser Lys Arg  
 355 360 365

His Ser Thr Ser Asp Leu Ser Asp Ala Thr Phe Ser Asp Ile Arg Arg  
 370 375 380

Glu Gly Trp Leu Tyr Tyr Lys Gln Ile Leu Thr Lys Lys Gly Lys Lys  
 385 390 395 400

Ala Gly Ser Gly Leu Arg Gln Trp Lys Arg Val Tyr Ala Ala Leu Arg  
 405 410 415

Ala Arg Ser Leu Ser Leu Ser Lys Glu Arg Arg Glu Pro Gly Pro Ala  
 420 425 430

Ala Ala Gly Ala Ala Ala Ala Gly Ala Gly Glu Asp Glu Ala Ala Pro  
 435 440 445

Val Cys Ile Gly Ser Cys Leu Val Asp Ile Ser Tyr Ser Glu Thr Lys  
 450 455 460

Arg Arg His Val Phe Arg Leu Thr Thr Ala Asp Phe Cys Glu Tyr Leu

681

465		470		475		480									
Phe	Gln	Ala	Glu	Asp	Arg	Asp	Asp	Met	Leu	Gly	Trp	Ile	Arg	Ala	Ile
				485					490					495	
Arg	Glu	Asn	Ser	Arg	Ala	Glu	Gly	Glu	Asp	Pro	Gly	Cys	Ala	Asn	Gln
			500					505					510		
Ala	Leu	Ile	Ser	Lys	Lys	Leu	Asn	Asp	Tyr	Arg	Lys	Val	Ser	His	Ser
		515					520					525			
Ser	Gly	Pro	Lys	Ala	Asp	Ser	Ser	Pro	Lys	Gly	Ser	Arg	Gly	Leu	Gly
	530					535						540			
Gly	Leu	Lys	Ser	Glu	Phe	Leu	Lys	Gln	Ser	Ala	Ala	Arg	Gly	Leu	Arg
545					550					555					560
Thr	Gln	Asp	Leu	Pro	Ala	Gly	Ser	Lys	Asp	Asp	Ser	Ala	Ala	Ala	Pro
			565						570					575	
Lys	Thr	Pro	Trp	Gly	Ile	Asn	Ile	Ile	Lys	Lys	Asn	Lys	Lys	Ala	Ala
		580					585							590	
Pro	Arg	Ala	Phe	Gly	Val	Arg	Leu	Glu	Glu	Cys	Gln	Pro	Ala	Thr	Glu
		595					600					605			
Asn	Gln	Arg	Val	Pro	Leu	Ile	Val	Ala	Ala	Cys	Cys	Arg	Ile	Val	Glu
	610					615					620				
Ala	Arg	Gly	Leu	Glu	Ser	Thr	Gly	Ile	Tyr	Arg	Val	Pro	Gly	Asn	Asn
625					630					635					640
Ala	Val	Val	Ser	Ser	Leu	Gln	Glu	Gln	Leu	Asn	Arg	Gly	Pro	Gly	Asp
			645						650					655	
Ile	Asn	Leu	Gln	Asp	Glu	Arg	Trp	Gln	Asp	Leu	Asn	Val	Ile	Ser	Ser
		660						665					670		
Leu	Leu	Lys	Ser	Phe	Phe	Arg	Lys	Leu	Pro	Glu	Pro	Leu	Phe	Thr	Asp
		675					680					685			
Asp	Lys	Tyr	Asn	Asp	Phe	Ile	Glu	Ala	Asn	Arg	Ile	Glu	Asp	Ala	Arg
	690					695					700				
Glu	Arg	Met	Arg	Thr	Leu	Arg	Lys	Leu	Ile	Arg	Asp	Leu	Pro	Gly	His
705					710					715					720



682

Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly His Leu Lys Thr Ile Ala  
725 730 735

Asp His Ser Glu Lys Asn Lys Met Glu Pro Arg Asn Leu Ala Leu Val  
740 745 750

Phe Gly Pro Thr Leu Val Arg Thr Ser Glu Asp Asn Met Thr Asp Met  
755 760 765

Val Thr His Met Pro Asp Arg Tyr Lys Ile Val Glu Thr Leu Ile Gln  
770 775 780

His Ser Asp Trp Phe Phe Ser Asp Glu Glu Asp Lys Gly Glu Arg Ile  
785 790 795 800

Leu Pro Pro Val Val Gln Pro Ser Pro Arg Val Arg Gly Pro Pro Arg  
805 810 815

Arg Ser Arg Thr Pro Gly Arg Cys Trp Arg Ser Pro Ser Arg Pro  
820 825 830

Ser Thr Ala Ser Ala Arg Ser Gly Gly Arg Arg Gly Gly Trp Ala Ala  
835 840 845

Ala Pro Thr Thr Thr Arg Ser Arg Arg Arg Thr Ser Leu Gly Arg Gly  
850 855 860

Pro Gln Arg Arg Gly Leu Arg Ser Gly Arg Arg Gly Ala Glu Ala Arg  
865 870 875 880

Arg Arg Arg Pro Leu Pro Arg Ala Ala Ala Thr Ala Ala Pro Gly Pro  
885 890 895

Gly Ser Pro Pro Ala Ala Arg Glu Gly Pro Pro Ala Ala Ala Thr Arg  
900 905 910

Ser Ile Val Ser Gly Tyr Ile Gln Pro Val Thr Met Asp Arg  
915 920 925

<210> 532

<211> 1011

<212> PRT

<213> Homo sapien

<400> 532

683

Met Ala Pro Arg Ala Arg Ser Ala Ser Gln Asp Arg Leu Glu Glu Val  
 1 5 10 15  
 Ala Ala Pro Arg Pro Trp Pro Cys Ser Thr Ser Gln Asp Ala Leu Ser  
 20 25 30  
 Gln Leu Gly Gln Glu Gly Trp His Arg Ala Arg Ser Asp Asp Tyr Leu  
 35 40 45  
 Ser Arg Ala Thr Arg Ser Ala Glu Ala Leu Gly Pro Gly Ala Leu Val  
 50 55 60  
 Ser Pro Arg Phe Glu Arg Cys Gly Trp Ala Ser Gln Arg Ser Ser Ala  
 65 70 75 80  
 Arg Thr Pro Ala Cys Pro Thr Arg Asp Leu Pro Gly Pro Gln Ala Pro  
 85 90 95  
 Thr Pro Ser Gly Leu Gln Gly Leu Asp Asp Leu Gly Tyr Ile Gly Tyr  
 100 105 110  
 Arg Ser Tyr Ser Pro Ser Phe Gln Arg Arg Thr Gly Leu Leu His Ala  
 115 120 125  
 Leu Ser Phe Arg Asp Ser Pro Phe Gly Gly Leu Pro Thr Phe Asn Leu  
 130 135 140  
 Ala Gln Ser Pro Ala Ser Phe Pro Pro Glu Ala Ser Glu Pro Pro Arg  
 145 150 155 160  
 Val Val Arg Pro Glu Pro Ser Thr Arg Ala Leu Glu Pro Pro Ala Glu  
 165 170 175  
 Asp Arg Gly Asp Glu Val Val Leu Arg Gln Lys Pro Pro Thr Gly Arg  
 180 185 190  
 Lys Val Gln Leu Thr Pro Ala Arg Gln Met Asn Leu Gly Phe Gly Asp  
 195 200 205  
 Glu Ser Pro Glu Pro Glu Ala Ser Gly Arg Gly Glu Arg Leu Gly Arg  
 210 215 220  
 Lys Val Ala Pro Leu Ala Thr Thr Glu Asp Ser Leu Ala Ser Ile Pro  
 225 230 235 240  
 Phe Ile Asp Glu Pro Thr Ser Pro Ser Ile Asp Leu Gln Ala Lys His

684

			245						250						255
Val	Pro	Ala	Ser	Ala	Val	Val	Ser	Ser	Ala	Met	Asn	Ser	Ala	Pro	Val
			260					265					270		
Leu	Gly	Thr	Ser	Pro	Ser	Ser	Pro	Thr	Phe	Thr	Phe	Thr	Leu	Gly	Arg
		275					280					285			
His	Tyr	Ser	Gln	Asp	Cys	Ser	Ser	Ile	Lys	Ala	Gly	Arg	Arg	Ser	Ser
	290					295					300				
Tyr	Leu	Leu	Ala	Ile	Thr	Thr	Glu	Arg	Ser	Lys	Ser	Cys	Asp	Asp	Gly
305					310					315					320
Leu	Asn	Thr	Phe	Arg	Asp	Glu	Gly	Arg	Val	Leu	Arg	Arg	Leu	Pro	Asn
				325					330					335	
Arg	Ile	Pro	Ser	Leu	Arg	Met	Leu	Arg	Ser	Phe	Phe	Thr	Asp	Gly	Ser
			340					345					350		
Leu	Asp	Ser	Trp	Gly	Thr	Ser	Glu	Asp	Ala	Asp	Ala	Pro	Ser	Lys	Arg
		355					360					365			
His	Ser	Thr	Ser	Asp	Leu	Ser	Asp	Ala	Thr	Phe	Ser	Asp	Ile	Arg	Arg
	370					375					380				
Glu	Gly	Trp	Leu	Tyr	Tyr	Lys	Gln	Ile	Leu	Thr	Lys	Lys	Gly	Lys	Lys
385					390					395					400
Ala	Gly	Ser	Gly	Leu	Arg	Gln	Trp	Lys	Arg	Val	Tyr	Ala	Ala	Leu	Arg
				405					410					415	
Ala	Arg	Ser	Leu	Ser	Leu	Ser	Lys	Glu	Arg	Arg	Glu	Pro	Gly	Pro	Ala
			420					425					430		
Ala	Ala	Gly	Ala	Ala	Ala	Ala	Gly	Ala	Gly	Glu	Asp	Glu	Ala	Ala	Pro
		435					440					445			
Val	Cys	Ile	Gly	Ser	Cys	Leu	Val	Asp	Ile	Ser	Tyr	Ser	Glu	Thr	Lys
	450					455					460				
Arg	Arg	His	Val	Phe	Arg	Leu	Thr	Thr	Ala	Asp	Phe	Cys	Glu	Tyr	Leu
465					470					475					480
Phe	Gln	Ala	Glu	Asp	Arg	Asp	Asp	Met	Leu	Gly	Trp	Ile	Arg	Ala	Ile
				485					490					495	

685

Arg Glu Asn Ser Arg Ala Glu Gly Glu Asp Pro Gly Cys Ala Asn Gln  
 500 505 510

Ala Leu Ile Ser Lys Lys Leu Asn Asp Tyr Arg Lys Val Ser His Ser  
 515 520 525

Ser Gly Pro Lys Ala Asp Ser Ser Pro Lys Gly Ser Arg Gly Leu Gly  
 530 535 540

Gly Leu Lys Ser Glu Phe Leu Lys Gln Ser Ala Ala Arg Gly Leu Arg  
 545 550 555 560

Thr Gln Asp Leu Pro Ala Gly Ser Lys Asp Asp Ser Ala Ala Ala Pro  
 565 570 575

Lys Thr Pro Trp Gly Ile Asn Ile Ile Lys Lys Asn Lys Lys Ala Ala  
 580 585 590

Pro Arg Ala Phe Gly Val Arg Leu Glu Glu Cys Gln Pro Ala Thr Glu  
 595 600 605

Asn Gln Arg Val Pro Leu Ile Val Ala Ala Cys Cys Arg Ile Val Glu  
 610 615 620

Ala Arg Gly Leu Glu Ser Thr Gly Ile Tyr Arg Val Pro Gly Asn Asn  
 625 630 635 640

Ala Val Val Ser Ser Leu Gln Glu Gln Leu Asn Arg Gly Pro Gly Asp  
 645 650 655

Ile Asn Leu Gln Asp Glu Arg Trp Gln Asp Leu Asn Val Ile Ser Ser  
 660 665 670

Leu Leu Lys Ser Phe Phe Arg Lys Leu Pro Glu Pro Leu Phe Thr Asp  
 675 680 685

Gly Ala Leu Leu Phe Tyr Leu Leu Asn Leu Gly Val His Val Leu Glu  
 690 695 700

Thr Gly Ala Gly Thr Pro Phe Leu Gly Ser Ala Cys Ser Ser Asp Gly  
 705 710 715 720

Ile Ala Ser Gln Met Asn Thr Ala Gly Leu Pro Gln Val Arg Cys Thr  
 725 730 735

686

Pro Glu Cys Ser Cys Asp Lys Tyr Asn Asp Phe Ile Glu Ala Asn Arg  
 740 745 750

Ile Glu Asp Ala Arg Glu Arg Met Arg Thr Leu Arg Lys Leu Ile Arg  
 755 760 765

Asp Leu Pro Gly His Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly His  
 770 775 780

Leu Lys Thr Ile Ala Asp His Ser Glu Lys Asn Lys Met Glu Pro Arg  
 785 790 795 800

Asn Leu Ala Leu Val Phe Gly Pro Thr Leu Val Arg Thr Ser Glu Asp  
 805 810 815

Asn Met Thr Asp Met Val Thr His Met Pro Asp Arg Tyr Lys Ile Val  
 820 825 830

Glu Thr Leu Ile Gln His Ser Asp Trp Phe Phe Ser Asp Glu Glu Asp  
 835 840 845

Lys Gly Glu Arg Thr Pro Val Gly Asp Lys Glu Pro Gln Ala Val Pro  
 850 855 860

Asn Ile Glu Tyr Leu Leu Pro Asn Ile Gly Arg Thr Val Pro Pro Gly  
 865 870 875 880

Asp Pro Gly Ser Asp Ser Thr Thr Cys Ser Ser Ala Lys Ser Lys Gly  
 885 890 895

Ser Trp Ala Pro Lys Lys Glu Pro Tyr Ala Arg Glu Met Leu Ala Ile  
 900 905 910

Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys Arg Arg Glu Ala  
 915 920 925

Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu Gln Glu Ala His  
 930 935 940

Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln Glu Arg Pro Pro  
 945 950 955 960

Gly Ser Arg Gly Pro Ala Ala Ala Ala Asp Ala Pro Arg Arg Arg His  
 965 970 975

687

Arg Gly Pro Arg Thr Arg Gln Ser Pro Gly Gly Ala Gly Gly Ala Ala  
                   980                                  985                                  990

Gly Arg Gly Asp Ala Leu His Cys Val Gly Leu Ile Gln Pro Val Thr  
                   995                                  1000                                  1005

Met Asp Arg  
                   1010

<210> 533  
 <211> 324  
 <212> PRT  
 <213> Homo sapien

<400> 533

Met Val Pro Phe Ser Ser Asp Leu Leu Asn Leu Gly Val His Val Leu  
   1                                  5                                  10                                  15

Glu Thr Gly Ala Gly Thr Pro Phe Leu Gly Ser Ala Cys Ser Ser Asp  
                   20                                  25                                  30

Gly Ile Ala Ser Gln Met Asn Thr Ala Gly Leu Pro Gln Val Arg Cys  
                   35                                  40                                  45

Thr Pro Glu Cys Ser Cys Asp Lys Tyr Asn Asp Phe Ile Glu Ala Asn  
                   50                                  55                                  60

Arg Ile Glu Asp Ala Arg Glu Arg Met Arg Thr Leu Arg Lys Leu Ile  
   65                                  70                                  75                                  80

Arg Asp Leu Pro Gly His Tyr Tyr Glu Thr Leu Lys Phe Leu Val Gly  
                   85                                  90                                  95

His Leu Lys Thr Ile Ala Asp His Ser Glu Lys Asn Lys Met Glu Pro  
                   100                                  105                                  110

Arg Asn Leu Ala Leu Val Phe Gly Pro Thr Leu Val Arg Thr Ser Glu  
                   115                                  120                                  125

Asp Asn Met Thr Asp Met Val Thr His Met Pro Asp Arg Tyr Lys Ile  
                   130                                  135                                  140

Val Glu Thr Leu Ile Gln His Ser Asp Trp Phe Phe Ser Asp Glu Glu  
   145                                  150                                  155                                  160

Asp Lys Gly Glu Arg Thr Pro Val Gly Asp Lys Glu Pro Gln Ala Val  
                   165                                  170                                  175

688

Pro Asn Ile Glu Tyr Leu Leu Pro Asn Ile Gly Arg Thr Val Pro Pro  
 180 185 190

Gly Asp Pro Gly Ser Asp Ser Thr Thr Cys Ser Ser Ala Lys Ser Lys  
 195 200 205

Gly Ser Trp Ala Pro Lys Lys Glu Pro Tyr Ala Arg Glu Met Leu Ala  
 210 215 220

Ile Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys Arg Arg Glu  
 225 230 235 240

Ala Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu Gln Glu Ala  
 245 250 255

His Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln Glu Arg Pro  
 260 265 270

Pro Gly Ser Arg Gly Pro Ala Ala Ala Asp Ala Pro Arg Arg Arg  
 275 280 285

His Arg Gly Pro Arg Thr Arg Gln Ser Pro Gly Gly Ala Gly Gly Ala  
 290 295 300

Ala Gly Arg Gly Asp Ala Leu His Cys Val Gly Leu Ile Gln Pro Val  
 305 310 315 320

Thr Met Asp Arg

<210> 534

<211> 269

<212> PRT

<213> Homo sapien

<400> 534

Met Met Arg Pro Trp Val Thr Gly Leu Gly Leu Gly Leu Asp Glu Arg  
 1 5 10 15

Leu Gly Ala Val Thr Trp Arg Gly Arg Thr Gly Asp Arg Arg Arg Gly  
 20 25 30

Arg Gln Arg Gly Arg Val Arg Asp Ala Pro Arg Ile Leu Asp Leu Ser  
 35 40 45

689

Pro Thr Gln Gly Ser Trp Ala Pro Lys Lys Glu Pro Tyr Ala Arg Glu  
 50 55 60

Met Leu Ala Ile Ser Phe Ile Ser Ala Val Asn Arg Lys Arg Lys Lys  
 65 70 75 80

Arg Arg Glu Ala Arg Gly Leu Gly Ser Ser Thr Asp Asp Asp Ser Glu  
 85 90 95

Gln Glu Ala His Lys Pro Gly Ala Gly Ala Thr Ala Pro Gly Thr Gln  
 100 105 110

Glu Arg Pro Leu Gly Pro Leu Pro Gly Ala Val Ala Pro Glu Ala Pro  
 115 120 125

Gly Arg Leu Ser Pro Pro Ala Ala Pro Glu Glu Arg Pro Ala Ala Asp  
 130 135 140

Thr Arg Ser Ile Val Ser Gly Tyr Ser Thr Leu Ser Thr Met Asp Arg  
 145 150 155 160

Ser Val Cys Ser Gly Ala Ser Gly Arg Arg Ala Gly Ala Gly Asp Glu  
 165 170 175

Ala Asp Asp Glu Arg Ser Glu Leu Ser His Val Glu Thr Asp Thr Glu  
 180 185 190

Gly Ala Ala Gly Ala Gly Pro Gly Gly Arg Leu Thr Arg Arg Pro Ser  
 195 200 205

Phe Ser Ser His His Leu Met Pro Cys Asp Thr Leu Ala Arg Arg Arg  
 210 215 220

Leu Ala Arg Gly Arg Pro Asp Gly Glu Gly Ala Gly Arg Gly Gly Pro  
 225 230 235 240

Arg Ala Pro Glu Pro Pro Gly Ser Ala Ser Ser Ser Ser Gln Glu Ser  
 245 250 255

Leu Arg Pro Pro Ala Ala Ala Leu Ala Ser Arg Pro Ser  
 260 265

<210> 535  
 <211> 325  
 <212> PRT  
 <213> Homo sapien



690

<220>  
 <221> MISC\_FEATURE  
 <222> (42)..(42)  
 <223> x= any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (44)..(44)  
 <223> x= any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (64)..(64)  
 <223> x= any amino acid

<400> 535

Met Glu Ser Trp Asn Trp Val Leu Val Phe Gly Cys Ile Leu Val Arg  
 1 5 10 15

Met Ser Glu Asp Asn Met Ile Asp Met Val Thr Tyr Met Leu Asp Cys  
 20 25 30

Tyr Lys Ile Val Glu Thr Leu Ile Gln Xaa Leu Xaa Trp Phe Phe Ser  
 35 40 45

Asp Glu Glu Asp Lys Gly Glu Arg Thr Leu Val Gly Asp Lys Glu Xaa  
 50 55 60

Gln Ala Val Pro Asn Ile Glu Tyr Leu Leu Pro Asn Ile Trp Gln Asp  
 65 70 75 80

Ser Ala Pro Trp Arg Pro Gly Val Ser Gly Pro Val Gly Asp Leu Lys  
 85 90 95

Asp Ser Thr Thr Cys Ser Ser Ala Lys Ser Lys Gly Ser Trp Ala Pro  
 100 105 110

Lys Lys Glu Pro Tyr Ala Arg Glu Met Leu Ala Ile Ser Phe Ile Ser  
 115 120 125

Ala Val Asn Arg Lys Arg Lys Lys Arg Arg Glu Ala Arg Gly Leu Gly  
 130 135 140

Ser Ser Thr Asp Asp Asp Ser Glu Gln Glu Ala His Lys Pro Gly Ala  
 145 150 155 160

Gly Ala Thr Ala Pro Gly Thr Gln Glu Arg Pro Leu Gly Pro Leu Pro

691

165

170

175

Gly Ala Val Ala Pro Glu Ala Pro Gly Arg Leu Ser Pro Pro Ala Ala  
 180 185 190

Pro Glu Glu Arg Pro Ala Ala Asp Thr Arg Ser Ile Val Ser Gly Tyr  
 195 200 205

Ser Thr Leu Ser Thr Met Asp Arg Ser Val Cys Ser Gly Ala Ser Gly  
 210 215 220

Arg Arg Ala Gly Ala Gly Asp Glu Ala Asp Asp Glu Arg Ser Glu Leu  
 225 230 235 240

Ser His Val Glu Thr Asp Thr Glu Gly Ala Ala Gly Ala Gly Pro Gly  
 245 250 255

Gly Arg Leu Thr Arg Arg Pro Ser Phe Ser Ser His His Leu Met Pro  
 260 265 270

Cys Asp Thr Leu Ala Arg Arg Arg Leu Ala Arg Gly Arg Pro Asp Gly  
 275 280 285

Glu Gly Ala Gly Arg Gly Gly Pro Arg Ala Pro Glu Pro Pro Gly Ser  
 290 295 300

Ala Ser Ser Ser Ser Gln Glu Ser Leu Arg Pro Pro Ala Ala Ala Leu  
 305 310 315 320

Ala Ser Arg Pro Ser  
 325

<210> 536

<211> 51

<212> PRT

<213> Homo sapien

<400> 536

Met Glu Leu Ser Ile Val Pro Val Thr Tyr Lys Thr Met Ser Pro Leu  
 1 5 10 15

His Ile His Phe Tyr Leu Leu Leu Trp Lys Ser Ala Val Asn Asn Asp  
 20 25 30

Ile Cys Thr Val Glu Ile Phe Phe Lys Val Leu Ala Pro Pro Pro Thr  
 35 40 45

692

Leu Val Val  
50

<210> 537  
<211> 41  
<212> PRT  
<213> Homo sapien

<400> 537

Met Asn Lys Thr Lys Phe Ser Leu Pro Asn Asp Phe Leu Ser His Leu  
1 5 10 15

Gly Asp Val Thr Leu Ala Ser Ser Leu Thr Pro Leu Ser Phe Ile Ile  
20 25 30

His Thr Asn Ser Leu Ala Gly Phe Thr  
35 40

<210> 538  
<211> 108  
<212> PRT  
<213> Homo sapien

<400> 538

Met Ala Lys Leu Asp Lys Asn Pro Gly Leu Leu Thr Pro Thr Arg Glu  
1 5 10 15

Pro Thr Pro Ser Thr Phe Ala Gly Arg His Val Met Asp Thr Thr Pro  
20 25 30

Glu Lys Gln Glu Pro Gly Val Arg Leu Glu Thr Cys Leu Arg Leu Ala  
35 40 45

Met Arg Asn Ala Pro Gly Arg His Glu Trp Pro Tyr Thr Phe Pro Pro  
50 55 60

Ser Pro Ala Pro Ser Phe Lys Val Pro Ile His Val Leu Ala Pro Ile  
65 70 75 80

Pro Leu Gly Ser Phe Gly Ala Ser His Leu His Thr Arg Thr His Thr  
85 90 95

Val Asn Trp Ala Leu Leu Ser Pro Cys Pro Val His  
100 105

<210> 539  
<211> 119

693

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 539

Arg Ala Phe Leu Asp Phe Val Cys Arg Thr Pro Ala Val Pro Phe Pro  
 1 5 10 15

Arg His Ser Pro Pro Glu His Thr Gly Arg Gly Gly Ser Pro Lys Thr  
 20 25 30

Trp Pro Pro Leu Ile Pro Val Leu Cys Val Ser Pro Phe Glu Phe Leu  
 35 40 45

Thr Ser Ser Ser Trp Val Leu Phe Leu Leu Ser Pro Phe Leu Phe Leu  
 50 55 60

Arg Lys Pro Gln Ala Ala Ser Pro Arg Ala Leu Val Trp Pro Glu Thr  
 65 70 75 80

Glu Ala Pro Arg Leu Glu Gly Gly Ala Ala Leu Gly Gly Pro Gly Gln  
 85 90 95

Trp Lys Ala Cys Tyr Tyr Leu Glu Trp Leu Leu Gly Pro Asn Thr Ser  
 100 105 110

Trp Glu Ala Gly Trp Val Lys  
 115

&lt;210&gt; 540

&lt;211&gt; 537

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 540

Met Glu Ser Gly Leu Ala Gly Asn Gly Thr Gly Ala Gly Leu Val Met  
 1 5 10 15

Lys Val Lys Gln Glu Lys Pro Glu Arg Leu Leu Gln Thr Leu Ala Pro  
 20 25 30

Gln Ala Met Leu Val Glu Lys Asp Lys Glu Asn Ile Phe Gln Gln His  
 35 40 45

Arg Gly Leu Pro Pro Arg Gln Thr Met Gly Arg Pro Arg Ala Leu Gly  
 50 55 60

Gly Gln Glu Glu Ser Gly Ser Pro Arg Trp Ala Pro Pro Thr Glu Gln

65				70				75				80				
Asp	Ala	Gly	Leu	Ala	Gly	Arg	Ala	Pro	Gly	Ser	Ala	Ser	Gly	Pro	Leu	
				85					90					95		
Ser	Pro	Ser	Leu	Ser	Ser	Gly	Glu	Gly	His	Phe	Val	Cys	Leu	Asp	Cys	
				100					105					110		
Gly	Lys	Arg	Phe	Ser	Trp	Trp	Ser	Ser	Leu	Lys	Ile	His	Gln	Arg	Thr	
				115					120					125		
His	Thr	Gly	Glu	Lys	Pro	Tyr	Leu	Cys	Gly	Lys	Cys	Gly	Lys	Ser	Phe	
				130					135					140		
Ser	Gln	Lys	Pro	Asn	Leu	Ala	Arg	His	Gln	Arg	His	His	Thr	Gly	Glu	
145					150					155					160	
Arg	Pro	Phe	Cys	Cys	Pro	Glu	Cys	Ala	Arg	Arg	Phe	Ser	Gln	Lys	Gln	
				165					170					175		
His	Leu	Leu	Lys	His	Gln	Lys	Thr	His	Ser	Arg	Pro	Ala	Thr	His	Ser	
				180					185					190		
Cys	Pro	Glu	Cys	Glu	Arg	Cys	Phe	Arg	His	Gln	Val	Gly	Leu	Arg	Ile	
				195					200					205		
His	Gln	Arg	Ala	His	Ala	Arg	Asp	Arg	Gln	Gly	Ser	Arg	Ala	Gly	Leu	
				210					215					220		
His	Glu	Leu	Ile	Gln	Asp	Ala	Ala	Ala	Arg	Arg	Ala	Cys	Arg	Leu	Gln	
225					230					235					240	
Pro	Gly	Pro	Pro	Arg	Gly	Arg	Pro	Glu	Trp	Ala	Trp	Leu	Gly	Leu	Cys	
				245					250					255		
Gln	Gly	Trp	Trp	Gly	Gln	Pro	Gly	Ala	Arg	Ala	Ala	Val	Ser	Gly	Pro	
				260					265					270		
Glu	Gly	Pro	Gly	Glu	Pro	Arg	Gln	Phe	Ile	Cys	Asn	Glu	Cys	Gly	Lys	
				275					280					285		
Ser	Phe	Thr	Trp	Trp	Ser	Ser	Leu	Asn	Ile	His	Gln	Arg	Ile	His	Thr	
				290					295					300		
Gly	Glu	Arg	Pro	Tyr	Ala	Cys	Pro	Glu	Cys	Gly	Arg	Arg	Phe	Ser	Gln	
305					310					315					320	

695

Lys Pro Asn Leu Thr Arg His Leu Arg Asn His Thr Gly Glu Arg Pro  
                   325                  330                  335

His Pro Cys Pro His Cys Gly Arg Gly Phe Arg Gln Lys Gln His Leu  
                   340                  345                  350

Leu Lys His Leu Arg Thr His Leu Pro Gly Ala Gln Ala Ala Pro Cys  
                   355                  360                  365

Pro Ser Cys Gly Lys Ser Cys Arg Ser Arg Ala Ala Leu Arg Ala His  
                   370                  375                  380

Gln Arg Ala His Ala Val Ala Glu Pro Ala Val Pro Ala Gly Glu Pro  
                   385                  390                  395                  400

Gly Asp Gln Pro Gln Ala Glu Ala Ile Pro Gly Leu Ala Ala Arg Pro  
                   405                  410                  415

Arg Ser Ser Gln Arg Ser Pro Gly Ala Arg Asp Thr Leu Trp Gly Arg  
                   420                  425                  430

Gly Gln Ala Gly Leu Ala Gly Pro Gly Glu Pro Arg Gln Phe Ile Cys  
                   435                  440                  445

Asn Glu Cys Gly Lys Ser Phe Ser Trp Trp Ser Ala Leu Thr Ile His  
                   450                  455                  460

Gln Arg Ile His Thr Gly Glu Arg Pro Tyr Pro Cys Pro Glu Cys Gly  
                   465                  470                  475                  480

Arg Arg Phe Ser Gln Lys Pro Asn Leu Thr Arg His Arg Arg Asn His  
                   485                  490                  495

Thr Gly Glu Arg Pro Tyr Leu Cys Pro Ala Cys Gly Arg Gly Phe Ser  
                   500                  505                  510

Gln Lys Gln His Leu Leu Lys His Gln Arg Val His Arg Ala Ala Pro  
                   515                  520                  525

Ala Cys Ser Pro Lys Glu Glu Ala Arg  
                   530                  535

<210> 541  
 <211> 68  
 <212> PRT

696

&lt;213&gt; Homo sapien

&lt;400&gt; 541

Met Glu Ser Gly Leu Ala Gly Asn Gly Thr Gly Ala Gly Leu Val Met  
 1 5 10 15

Lys Val Lys Gln Glu Lys Pro Glu Arg Leu Leu Gln Thr Leu Ala Pro  
 20 25 30

Gln Ala Met Leu Val Glu Lys Asp Lys Glu Asn Val Leu Trp Thr Thr  
 35 40 45

Leu Val Phe Phe Phe Ala Cys Gly Ser Phe Lys Leu Leu Val Phe Lys  
 50 55 60

Ile Ser Thr Phe  
 65

&lt;210&gt; 542

&lt;211&gt; 550

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 542

Met Leu Asp Leu Met Leu Glu Ala Val Asn Asn Ile Lys Asp Ala Met  
 1 5 10 15

Pro Lys Met Gln Ile Gly Ala Pro Val Gln Ala Ile Thr Leu Met Ser  
 20 25 30

Gly Glu Arg Pro Cys Leu Gln Gly Tyr Tyr Thr Ala Ala Val Ile Asp  
 35 40 45

Ser Leu Ser Leu Thr Val His Leu Arg Ile Leu Asn Ala Pro Gly Ala  
 50 55 60

Ser Gly Asn Ser Ile Gln Asp Tyr Thr Asn Leu Ser Val Val Arg Ala  
 65 70 75 80

Lys Gly Asn Lys Asp Val Gly Lys Ser Lys His Cys Phe Asn Ala Phe  
 85 90 95

Ala Ser Asp Arg Ser Ser Leu His Arg Asp Leu Gly Pro Asp Thr Arg  
 100 105 110

Pro Pro Glu Cys Ile Val Leu Tyr Asn Phe Lys Arg Cys Gly Lys Arg  
 115 120 125

Phe Ser Trp Trp Ser Ser Leu Lys Ile His Gln Arg Thr His Thr Gly  
 130 135 140

Glu Lys Pro Tyr Leu Cys Gly Lys Cys Gly Lys Ser Phe Ser Gln Lys  
 145 150 155 160

Pro Asn Leu Ala Arg His Gln Arg His His Thr Gly Glu Arg Pro Phe  
 165 170 175

Cys Cys Pro Glu Cys Ala Arg Arg Phe Ser Gln Lys Gln His Leu Leu  
 180 185 190

Lys His Gln Lys Thr His Ser Arg Pro Ala Thr His Ser Cys Pro Glu  
 195 200 205

Cys Glu Arg Cys Phe Arg His Gln Val Gly Leu Arg Ile His Gln Arg  
 210 215 220

Ala His Ala Arg Asp Arg Gln Gly Ser Arg Ala Gly Leu His Glu Leu  
 225 230 235 240

Ile Gln Asp Ala Ala Ala Arg Arg Ala Cys Arg Leu Gln Pro Gly Pro  
 245 250 255

Pro Arg Gly Arg Pro Glu Trp Ala Trp Leu Gly Leu Cys Gln Gly Trp  
 260 265 270

Trp Gly Gln Pro Gly Ala Arg Ala Ala Val Ser Gly Pro Glu Gly Pro  
 275 280 285

Gly Glu Pro Arg Gln Phe Ile Cys Asn Glu Cys Gly Lys Ser Phe Thr  
 290 295 300

Trp Trp Ser Ser Leu Asn Ile His Gln Arg Ile His Thr Gly Glu Arg  
 305 310 315 320

Pro Tyr Ala Cys Pro Glu Cys Gly Arg Arg Phe Ser Gln Lys Pro Asn  
 325 330 335

Leu Thr Arg His Leu Arg Asn His Thr Gly Glu Arg Pro His Pro Cys  
 340 345 350

Pro His Cys Gly Arg Gly Phe Arg Gln Lys Gln His Leu Leu Lys His  
 355 360 365



698

Leu Arg Thr His Leu Pro Gly Ala Gln Ala Ala Pro Cys Pro Ser Cys  
 370 375 380

Gly Lys Ser Cys Arg Ser Arg Ala Ala Leu Arg Ala His Gln Arg Ala  
 385 390 395 400

His Ala Val Ala Glu Pro Ala Val Pro Ala Gly Glu Pro Gly Asp Gln  
 405 410 415

Pro Gln Ala Glu Ala Ile Pro Gly Leu Ala Ala Arg Pro Arg Ser Ser  
 420 425 430

Gln Arg Ser Pro Gly Ala Arg Asp Thr Leu Trp Gly Arg Gly Gln Ala  
 435 440 445

Gly Leu Ala Gly Pro Gly Glu Pro Arg Gln Phe Ile Cys Asn Glu Cys  
 450 455 460

Gly Lys Ser Phe Ser Trp Trp Ser Ala Leu Thr Ile His Gln Arg Ile  
 465 470 475 480

His Thr Gly Glu Arg Pro Tyr Pro Cys Pro Glu Cys Gly Arg Arg Phe  
 485 490 495

Ser Gln Lys Pro Asn Leu Thr Arg His Arg Arg Asn His Thr Gly Glu  
 500 505 510

Arg Pro Tyr Leu Cys Pro Ala Cys Gly Arg Gly Phe Ser Gln Lys Gln  
 515 520 525

His Leu Leu Lys His Gln Arg Val His Arg Ala Ala Pro Ala Cys Ser  
 530 535 540

Pro Lys Glu Glu Ala Arg  
 545 550

<210> 543  
 <211> 198  
 <212> PRT  
 <213> Homo sapien

<400> 543

Met Glu Ser Gly Leu Ala Gly Asn Gly Thr Gly Ala Gly Leu Val Met  
 1 5 10 15

Lys Val Lys Gln Glu Lys Pro Glu Arg Leu Leu Gln Thr Leu Ala Pro

699

20 25 30  
 Gln Ala Met Leu Val Glu Lys Asp Lys Glu Asn Ile Phe Gln Gln His  
 35 40 45  
 Arg Gly Leu Pro Pro Arg Gln Thr Met Gly Arg Pro Arg Ala Leu Gly  
 50 55 60  
 Gly Gln Glu Glu Ser Gly Ser Pro Arg Trp Ala Pro Pro Thr Glu Gln  
 65 70 75 80  
 Asp Ala Gly Leu Ala Gly Arg Ala Pro Gly Ser Ala Ser Gly Pro Leu  
 85 90 95  
 Ser Pro Ser Leu Ser Ser Gly Glu Gly His Phe Val Cys Leu Asp Cys  
 100 105 110  
 Gly Lys Arg Phe Ser Trp Trp Ser Ser Leu Lys Ile His Gln Arg Thr  
 115 120 125  
 His Thr Gly Glu Lys Pro Tyr Leu Cys Gly Lys Cys Gly Lys Ser Phe  
 130 135 140  
 Ser Gln Lys Pro Asn Leu Ala Arg His Gln Arg His His Thr Gly Glu  
 145 150 155 160  
 Arg Pro Phe Cys Cys Pro Glu Cys Ala Arg Arg Phe Ser Gln Lys Gln  
 165 170 175  
 His Leu Leu Lys His Gln Arg Val His Arg Ala Ala Pro Ala Cys Ser  
 180 185 190  
 Pro Lys Glu Glu Ala Arg  
 195  
 <210> 544  
 <211> 20  
 <212> PRT  
 <213> Homo sapien  
 <400> 544  
 Met Lys Leu Ile Ser Phe Ser Leu Met Leu Trp Leu Arg Val Asn Ala  
 1 5 10 15  
 Leu Tyr Leu Cys  
 20

700

<210> 545  
 <211> 52  
 <212> PRT  
 <213> Homo sapien

<400> 545

Met His Cys Arg Gln Trp Glu Asn Lys Tyr Ser Met Asn Val Ser Glu  
 1 5 10 15

Lys Arg Lys Lys Arg Gly Leu Phe Val Tyr Tyr Ser Phe Lys Trp Lys  
 20 25 30

Asp Gln Gly His Gly Met Asn Tyr Ile Phe His Ile Leu Cys Ile Ser  
 35 40 45

Tyr Leu Phe Leu  
 50

<210> 546  
 <211> 67  
 <212> PRT  
 <213> Homo sapien

<400> 546

Met Leu Ile Lys Gln Ala Gly Val Arg Met Glu Asn Ala Ser Ile Arg  
 1 5 10 15

Lys Arg Thr His Lys Cys Leu Ala Ser Leu His Arg Val Phe Pro Leu  
 20 25 30

Leu Ser Ser Trp Ser Ser Pro Leu Gly Arg Asn Ser Pro Leu Gly His  
 35 40 45

Val Trp Ala Leu Ala Ser Ser Lys Leu Leu Tyr Pro Ser Ser Gly Glu  
 50 55 60

Asn Ser Leu  
 65

<210> 547  
 <211> 118  
 <212> PRT  
 <213> Homo sapien

<400> 547

Met Ala Glu Gln Ala Ser His Tyr Tyr Ala Arg Leu Gly Gly Ala  
 1 5 10 15

701

Arg Gln Lys Ile Ala Leu Gly Asp Thr Cys Leu Val Cys Arg Asp Pro  
                   20                  25                  30

Gln Gly Thr Ser Arg Val Leu Glu His Leu Leu Val Ser Phe Phe Leu  
           35                  40                  45

Glu Leu Ser Tyr Phe Tyr Pro Lys Thr Asp Arg Ser Tyr Val Asn Leu  
       50                  55                  60

His Leu Lys Lys Asp Ile Ala Phe Phe Pro Ser Ala Ser Gln Ile Cys  
   65                  70                  75                  80

Ser Asn Thr Asn Ser Leu Ala Phe Asp Phe Ile Ile Met Ile Val His  
                   85                  90                  95

Gln Pro Phe Phe Thr Lys Asn Pro His Ile Met Ser Tyr Lys Gly Phe  
           100                  105                  110

Ile Ile Phe Asn Gly Lys  
       115

<210> 548

<211> 115

<212> PRT

<213> Homo sapien

<400> 548

Met Gly Thr Glu Tyr Ser Ile Ala Leu Gln Met Ser Asn Ile Phe Lys  
   1                  5                  10                  15

Ala Met Leu Ser Asn Asn Val Tyr Thr Glu Asn Arg Met His Arg Phe  
           20                  25                  30

Asn Ile Asp Ser Asn Val Tyr Val Gly Ser Phe Val Gly Asp Cys Lys  
       35                  40                  45

Leu Tyr Val Pro Pro Val Leu Leu Gly Phe Val Gly Lys Leu Lys Glu  
       50                  55                  60

Asn Leu Val Leu Ser Leu Ile Met Lys Phe Ile Ala Asn Leu Glu Arg  
   65                  70                  75                  80

Glu Asn Asn Leu Lys Thr Lys Ile Pro His Ser Ser Glu Asp Ala Trp  
           85                  90                  95

Asn Lys Ile Trp Asn Ser Ser Val Pro Thr Ser Pro Leu Gln Thr Phe

702

100

105

110

Leu Leu Phe  
115

<210> 549  
<211> 63  
<212> PRT  
<213> Homo sapien

<400> 549

Met Lys Glu Ser Ile Val Arg His Tyr Ser Lys Lys Asn Phe Leu Thr  
1 5 10 15

Cys Leu Ser Trp Lys Ser Thr Lys Gly His Leu Ser Cys Leu Asp Met  
20 25 30

Asp Tyr Gln Tyr Val Cys Ile Gln His Thr Ala Tyr Lys Val Arg Gly  
35 40 45

Asn Asn Arg Gln Tyr Ile Leu Cys Thr His Asn Tyr Ser Pro Pro  
50 55 60

<210> 550  
<211> 57  
<212> PRT  
<213> Homo sapien

<400> 550

Met Leu Phe Gly Thr Ile Lys Tyr Gln Ile Ile Ser Lys Lys Pro Met  
1 5 10 15

Val Ser Trp Leu Cys Trp Cys Pro Ser Leu Thr Phe Val Ser Ser Trp  
20 25 30

Gly Ser Arg Leu Ala Gly Cys Ser Ser Ser Leu Gln Asp Gly Ser Cys  
35 40 45

Gly Pro Leu Ser His His Thr Gly Leu  
50 55

<210> 551  
<211> 41  
<212> PRT  
<213> Homo sapien

<400> 551

Met Ser Thr Phe Ser Ser Asp Leu Thr Ser Val Ser Thr Cys Leu Leu

703

1                      5                      10                      15

Asp Ile Tyr Ile Tyr Leu Asp Met Ser Cys Gly Tyr Val Pro Arg Gln  
20                      25                      30

His Ile Gln Lys Leu Thr His Tyr Leu  
35                      40

<210> 552  
<211> 92  
<212> PRT  
<213> Homo sapien

<400> 552

Met Leu Tyr Ser Phe Leu Asn Tyr Leu Asp Ile Ser Ser Ile Lys Leu  
1                      5                      10                      15

Trp Pro Cys Val Pro Leu Gln Gly Ser Ser Ser Glu Met Thr Leu Ile  
20                      25                      30

Ser Cys Cys Ser Met Tyr Gln Ile His Ser Leu Val Tyr Cys Leu Asp  
35                      40                      45

Val Ser Thr Leu Cys Leu Gly Met Ile Cys Leu Thr Glu Met Asn Tyr  
50                      55                      60

Ile Tyr Val Pro Lys Ser Leu Ser Asn Phe Asn Ser Lys Tyr Ile Thr  
65                      70                      75                      80

Ser Ser Ser Ile Gly Tyr Leu Phe His Ser Ala Phe  
85                      90

<210> 553  
<211> 67  
<212> PRT  
<213> Homo sapien

<400> 553

Met Ile Phe Lys Arg Thr Phe Lys Ile Ser Thr His Leu Thr Thr Ile  
1                      5                      10                      15

Leu Ser Arg Leu Cys Thr His Val Leu Gly Lys Leu Gln Lys Asn Gly  
20                      25                      30

Arg Lys Lys Gly Pro Lys Ser Thr Lys His Arg Arg His Asn Ser Lys  
35                      40                      45

704

Asn Ile Gln Tyr Tyr Cys Ser Lys Leu Leu Asn Lys Cys Ser Leu Thr  
 50 55 60

Glu Asn His  
 65

<210> 554  
 <211> 57  
 <212> PRT  
 <213> Homo sapien  
 <400> 554

Met Ala Asp Thr Val Ser Phe Ala Pro Ser Thr Ser Pro Ile Ser Leu  
 1 5 10 15

Phe Phe Tyr Glu Cys Leu Pro Ser Pro Thr Pro Tyr Ala Pro Val Gly  
 20 25 30

Phe His His Phe Ala Leu Phe Val Gln Lys Gly Val Pro Gly Leu Val  
 35 40 45

Lys Gln Gly Pro Pro Ser Phe Cys Leu  
 50 55

<210> 555  
 <211> 73  
 <212> PRT  
 <213> Homo sapien  
 <400> 555

Met Ser Val Gly Leu Met Asn His Leu Lys Leu Phe Lys Ser Arg Ala  
 1 5 10 15

Glu Ala Ser Leu Lys Lys Glu Ile Ala Pro Phe Ser Ser Ile Phe Leu  
 20 25 30

Ser Trp Val Ser Val Pro Ser Glu Pro Ser Trp Gly Ile Ala Ile Cys  
 35 40 45

Phe Leu Gln Leu Leu Ser Gln Ser His Ser Gly Ile Arg Lys Phe Leu  
 50 55 60

Ala Ile Asn His Leu Tyr Met Ser Tyr  
 65 70

<210> 556  
 <211> 43  
 <212> PRT

705

&lt;213&gt; Homo sapien

&lt;400&gt; 556

Met Ser Phe Pro Leu Ile Met Lys His Ser Leu Lys Leu Phe Trp Tyr  
 1 5 10 15

Val Ile Ile Leu Leu Tyr Ser Leu Tyr Thr Val Glu Asn Lys Phe Ser  
 20 25 30

Ser Gly Ile Leu Val Ser Ser Ser Phe Ser Pro  
 35 40

&lt;210&gt; 557

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 557

Met Ala Ser Gln Tyr Leu Leu Cys Ile Phe Lys Gln Ile Lys Asn Val  
 1 5 10 15

Ile Leu Thr Phe Ala Tyr Gly His Ser Tyr Asp Tyr Thr Glu Arg Asp  
 20 25 30

Gly Ile Ile Leu Thr Cys Leu Ile His Gly Leu Phe Leu Val Asn Asn  
 35 40 45

Asn Ile Thr Thr Gln Arg Lys Gly Asn Val Tyr Ile Leu Lys Asn Tyr  
 50 55 60

Cys Gln Leu His Leu Val Phe Phe Arg Leu Cys Ile Lys  
 65 70 75

&lt;210&gt; 558

&lt;211&gt; 61

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 558

Met Ala Gly Ser Trp Val Ala Glu Ser Pro Pro Leu Gly Ala Gly Arg  
 1 5 10 15

Ser Glu Cys Gln Pro Ser Ala Leu Ile Asn Leu Pro Asn His Leu Ile  
 20 25 30

Ser Leu Ser Leu Ile Val Pro Ile Cys Phe Asn Gly Glu Gln Pro His  
 35 40 45



706

Val Ile Leu Pro Asn Leu Ala Glu Ser Leu Arg Ile Ser  
50 55 60

<210> 559  
<211> 59  
<212> PRT  
<213> Homo sapien

<400> 559

Ala Ala Ala Gly Ser Gly Val Arg Ser Arg Asp Ala Val Val Gly Ala  
1 5 10 15

Gly Gln Arg Arg Ala Pro Glu Ala Gly Ala Ala Gly Gly Arg Ala Asn  
20 25 30

Val Ile Phe Pro Asn Lys Leu Phe Pro Ala Glu Ser Ser Leu Leu Ala  
35 40 45

Gln Asn Lys Gln Met Lys Ser Ser Pro Glu Arg  
50 55

<210> 560  
<211> 55  
<212> PRT  
<213> Homo sapien

<400> 560

Ala Ala Ala Gly Ser Gly Val Arg Ser Arg Asp Ala Val Val Gly Ala  
1 5 10 15

Gly Gln Arg Arg Ala Pro Glu Ala Gly Ala Ala Gly Gly Arg Ala Asn  
20 25 30

Val Ile Phe Pro Asn Lys Leu Phe Pro Ala Glu Ser Ser Leu Leu Ala  
35 40 45

Gln Asn Lys Gln Met Lys Arg  
50 55

<210> 561  
<211> 72  
<212> PRT  
<213> Homo sapien

<400> 561

Met Pro Cys Thr Val Ser Pro Ser Gln Gln Pro Arg Leu Gln Met Asp  
1 5 10 15

707

Leu Pro Cys Ser Phe Pro Cys Pro Leu Asp Ser Trp Ser Ala Gly Leu  
                   20                                  25                                  30

Val Val Cys Pro Ala Leu Cys Gln Ala Ala Trp Arg Arg Gly His Leu  
                   35                                  40                                  45

Ala Ala Pro Leu Gly Phe Phe His Ala Thr Leu Val His Leu Ser Phe  
                   50                                  55                                  60

Leu Ser Gly Ala Gly Pro Arg Ile  
   65                                  70

<210> 562  
 <211> 121  
 <212> PRT  
 <213> Homo sapien

<400> 562

Met Thr Pro Pro Ala Phe Pro Leu Thr Ile Phe Ser Arg Asp Pro Pro  
   1                                  5                                  10                                  15

Leu Leu Leu Gly Pro Lys Glu Glu Arg Gly Arg Lys Phe His Thr Pro  
                   20                                  25                                  30

Ser Lys Ala Arg Gly His Arg Arg Gly Gly Ser Arg Gln Ala Gly Ala  
                   35                                  40                                  45

Arg Cys Pro Ser Leu Gly Ala Ser Glu Gly His Thr Val Ala Arg Gln  
                   50                                  55                                  60

Pro Leu Leu Pro Leu Leu Pro Thr Trp Arg Pro Val Ala Lys Ala Phe  
   65                                  70                                  75                                  80

Val Pro Gly Ser Glu Glu Leu Ala Val Leu Ala Ala Thr Pro Val His  
                   85                                  90                                  95

Gly Phe Pro Leu Ala Ser Ser Pro Arg Glu Phe Trp Leu Arg Glu Gly  
                   100                                  105                                  110

Val Arg Glu Glu Arg Lys Gly Thr Leu  
                   115                                  120

<210> 563  
 <211> 57  
 <212> PRT  
 <213> Homo sapien

708

&lt;400&gt; 563

Met Gln Leu Lys Val Ser Gln Phe Ile Pro Arg Ile Ser His His Leu  
 1 5 10 15

Gln Ala Pro Tyr Leu Asp Gly Ser Leu Ala Cys His Phe Phe Phe Phe  
 20 25 30

Ser Pro Asn Val Thr Phe Ser Val Arg Ile Ser Leu Thr Ser Pro Phe  
 35 40 45

Lys Ile Ala Thr Ser Thr Ser Thr Leu  
 50 55

&lt;210&gt; 564

&lt;211&gt; 321

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 564

Phe Val Ser Leu Cys Ser Gly Ser Ser Ser Cys Arg Ser Leu Leu Phe  
 1 5 10 15

Phe Phe Arg Phe Val Leu Ile Arg Trp Ser Phe Pro Leu Leu Ser Ser  
 20 25 30

Ser Phe Ser Ser Ser Leu Phe Val Val Leu Phe Arg Arg Cys Gly Leu  
 35 40 45

Val Arg Phe Ser Arg Ser Val Leu Ala Ser Val Leu Leu Ala Leu Leu  
 50 55 60

Leu Leu Ser Ser Cys Val Arg Phe Pro Val Ala Cys Leu Ser Phe Ser  
 65 70 75 80

Leu Leu Leu Val Ile Cys Phe Ser Leu Phe Leu Leu Phe Leu Ser Pro  
 85 90 95

Val Ser Pro Ser Phe Leu Val Ser Ser Ser Pro Phe Leu Leu Phe Ala  
 100 105 110

Cys Ala Cys Leu Ala Arg Ser Val Phe Phe Cys Leu Cys Phe Cys Arg  
 115 120 125

Val Arg Leu Ser Leu Val Phe Phe Gly Leu Leu Phe Leu Phe Ser Pro  
 130 135 140

709

Leu Arg Ser Leu Leu Phe Ser Val Leu Arg Ala Ser Val Pro Phe Val  
 145 150 155 160

Phe Phe Val Phe Phe Ala Ser Phe Arg Ser Leu Arg Ser Ser Ser Ser  
 165 170 175

Val Pro Leu Leu Ser Ser Phe Leu Pro Leu Ser Pro Phe Leu Leu Leu  
 180 185 190

Trp Leu Pro Ser Leu Ala Val Leu Pro Leu Arg Leu Pro Leu Leu Pro  
 195 200 205

Ser Val Val Ser Arg Cys Cys Ser Cys Val Leu Leu Cys Val Leu Val  
 210 215 220

Leu Phe Trp Phe Leu Val Gly Gly Cys Val Val Cys Ala Leu Cys Val  
 225 230 235 240

Leu Phe Val Val Phe Val Arg Ser Trp Cys Thr Ala Glu Lys Ser His  
 245 250 255

His Gln Arg Thr Ser Phe Asn Arg Leu Ile Val Gly Ala Ser Pro Glu  
 260 265 270

Gly Leu Arg Ala Gly Arg Ser Gly Gly Cys Ser Arg Leu Leu Phe Phe  
 275 280 285

Ala Pro Trp Ala Leu Ser Lys Arg Ser Arg Tyr Leu Ala Leu Glu Gly  
 290 295 300

Thr Leu Ala Pro Pro Phe Phe Phe Cys Met Ser Thr Phe Ala Phe Ile  
 305 310 315 320

Glu

&lt;210&gt; 565

&lt;211&gt; 149

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 565

Met His Gln Arg Pro Pro Thr Leu Pro Arg Ile Ala Phe Met Ile Glu  
 1 5 10 15

Leu Lys Leu Leu Lys Val Ile His Ser Pro His Asp Arg Ala Val Pro  
 20 25 30

710

Pro Ser Leu Pro Leu Cys Leu Trp Ala Pro Glu Ala Pro Leu Ile Pro  
 35 40 45

Gly Arg Phe Leu Pro Pro Cys Leu His Ser Ser Leu Leu Ser Pro Leu  
 50 55 60

Phe Leu Lys Leu Leu Phe Leu Thr Leu Leu Glu Ala Arg Leu Asp Asp  
 65 70 75 80

Trp Leu Asn Thr Leu Tyr Leu Arg Glu Arg Leu Tyr Leu Lys Phe Glu  
 85 90 95

Ile Leu Cys Thr Ser Tyr Asn Ala Gly Cys Thr Leu Ser Arg Ile Pro  
 100 105 110

Ser Leu Ser Ser Ser Cys Ser Ser Leu His Thr Arg Gln Ala Gly Val  
 115 120 125

Pro Cys Leu Ser Ser Leu Phe His Ala Ser His Lys Cys Tyr Val Trp  
 130 135 140

Ile Leu Leu Pro His  
 145

<210> 566

<211> 387

<212> PRT

<213> Homo sapien

<400> 566

Met Arg Ser Val Ser Tyr Val Gln Arg Val Ala Leu Glu Phe Ser Gly  
 1 5 10 15

Ser Leu Phe Pro His Ala Ile Cys Leu Gly Asp Val Asp Asn Asp Thr  
 20 25 30

Leu Asn Glu Leu Val Val Gly Asp Thr Ser Gly Lys Val Ser Val Tyr  
 35 40 45

Lys Asn Asp Asp Ser Arg Pro Trp Leu Thr Cys Ser Cys Gln Gly Met  
 50 55 60

Leu Thr Cys Val Gly Val Gly Asp Val Cys Asn Lys Gly Lys Asn Leu  
 65 70 75 80

Leu Val Ala Val Ser Ala Glu Gly Trp Phe His Leu Phe Asp Leu Thr  
85 90 95

Glu Glu Val Val Ala Cys Ala Trp Asp Gly Gln Thr Tyr Ile Ile Asp

712

325

330

335

His Asn Arg Thr Val Val Arg Phe Gln Val Asp Glu Asn Ile Arg Ala  
 340 345 350

Phe Cys Ala Gly Asp Pro Arg Pro His Gly Pro Phe Leu Thr Thr Leu  
 355 360 365

Lys Leu Asp Arg Arg Val Arg His Ala Arg Glu Val Phe Ala Pro His  
 370 375 380

Phe Pro Phe  
 385

<210> 567  
 <211> 31  
 <212> PRT  
 <213> Homo sapien

<400> 567

Glu Gly Gly Ala Glu Glu Gln His Gly Arg Glu Pro Val Ser Asp Lys  
 1 5 10 15

Lys Thr Lys Thr Gln Lys Leu Asn Gly Lys Val Arg Ser Leu Asn  
 20 25 30

<210> 568  
 <211> 178  
 <212> PRT  
 <213> Homo sapien

<400> 568

Met Arg Ser Val Ser Tyr Val Gln Arg Val Ala Leu Glu Phe Ser Gly  
 1 5 10 15

Ser Leu Phe Pro His Ala Ile Cys Leu Gly Asp Val Asp Asn Asp Thr  
 20 25 30

Leu Asn Glu Leu Val Val Gly Asp Thr Ser Gly Lys Val Ser Val Tyr  
 35 40 45

Lys Asn Asp Asp Ser Arg Pro Trp Leu Thr Cys Ser Cys Gln Gly Met  
 50 55 60

Leu Thr Cys Val Gly Val Gly Asp Val Cys Asn Lys Gly Lys Asn Leu  
 65 70 75 80

713

Leu Val Ala Val Ser Ala Glu Gly Trp Phe His Leu Phe Asp Leu Thr  
                             85                            90                            95

Pro Ala Lys Val Leu Asp Ala Ser Gly His His Glu Thr Leu Ile Gly  
                             100                            105                            110

Glu Glu Gln Arg Pro Val Phe Lys Gln His Ile Pro Ala Asn Thr Lys  
                             115                            120                            125

Val Met Leu Ile Ser Asp Ile Val Gly Met Pro Thr Phe Ala Gly Ser  
                             130                            135                            140

Gln Glu Ser Arg Ser Gln Trp Ile Leu Glu His Ile Pro Arg Asp Trp  
                             145                            150                            155                            160

Gly Glu Arg Glu Asn Pro Tyr Ser Cys Met His Leu Leu Cys Ala Glu  
                             165                            170                            175

Leu Pro

<210> 569  
 <211> 90  
 <212> PRT  
 <213> Homo sapien  
 <400> 569

Met His Gln Arg Leu Ser Lys Ser Tyr Leu Arg Pro Gln Leu Leu Pro  
   1                            5                            10                            15

Arg Thr Gln Val Val Glu Ile Ile Cys Arg Leu Asn Ile Ser Thr Trp  
                             20                            25                            30

Phe Gln Gln Ala Pro Gln Ile Gln His Ile Gln Asn Arg Ser Phe Tyr  
                             35                            40                            45

Phe Leu Ser Ala Lys Pro Thr Pro Val Pro Glu His Ile Ser Gly Asn  
                             50                            55                            60

Ser Ala Ile Arg Asn Ser Tyr Phe Ile Cys Ser Leu Tyr His Leu Thr  
   65                            70                            75                            80

Leu Thr Pro Leu Ile Ile Leu Ser Thr His  
                             85                            90

<210> 570  
 <211> 43



714

<212> PRT  
 <213> Homo sapien

<400> 570

Met Val Leu Phe Leu Ile Val Tyr Phe Leu Asp Asn Asp Ser Ser Glu  
 1 5 10 15

Lys Phe Arg Pro Phe Val Phe Phe Phe Asn Pro Ala Pro Ser Val Lys  
 20 25 30

Thr Met Ser Tyr Arg Met Ser Cys Phe Trp Ile  
 35 40

<210> 571  
 <211> 55  
 <212> PRT  
 <213> Homo sapien

<400> 571

Met Gln Leu Ser Lys Ser Ser Leu Phe Pro Ser His Leu Gln Leu Asn  
 1 5 10 15

Thr Ile Ser Gln Phe Leu Phe Leu Asp Thr Ala Arg Asn Arg Pro Ser  
 20 25 30

Tyr Gln Ser Ser His Phe Leu Ser Val Ser Phe Pro Asn Ser Phe Ser  
 35 40 45

Gln Asn Leu Leu Gln Ile Ser  
 50 55

<210> 572  
 <211> 60  
 <212> PRT  
 <213> Homo sapien

<400> 572

Met Leu Thr Glu Leu Leu Phe Thr Ile Tyr Phe His Ile Tyr Lys Trp  
 1 5 10 15

Glu Tyr Ser Ser Ser Ile Thr Phe Cys Asn Asp His Val Ile Thr Val  
 20 25 30

Gly Lys Tyr Pro Tyr Asp Lys Leu Glu Ser Leu Cys Ser Ile Val Cys  
 35 40 45

Ile Arg Ile Ser Leu Ile Phe Ser Ile Ser Ser Gln  
 50 55 60

715

<210> 573  
 <211> 51  
 <212> PRT  
 <213> Homo sapien

<400> 573

Met Asn Cys Thr Gln Ala Ile Ala Glu Asp Gly Ile Val Ser Tyr Pro  
 1 5 10 15

Tyr Asn Leu Glu Asn Ser Pro Trp Arg Gln Asn Pro Asp Leu Leu Arg  
 20 25 30

Lys Leu Gly Leu Leu Asp Ser Arg Gln Arg Ile Val Phe Pro Asn Tyr  
 35 40 45

Cys Phe Leu  
 50

<210> 574  
 <211> 56  
 <212> PRT  
 <213> Homo sapien

<400> 574

Met Ala Leu Leu Glu Leu Leu Thr Ser Asn Phe Arg Phe Asp Ser Phe  
 1 5 10 15

Tyr Lys Gln Phe Phe Pro Leu Val Cys Pro Met Ser Arg Arg Pro Phe  
 20 25 30

Pro Val Arg Tyr Leu Cys Met Ser His Ala Ile Cys Asn Ser Ser Cys  
 35 40 45

Met Asp Ala Ser Ala Ile His Thr  
 50 55

<210> 575  
 <211> 728  
 <212> PRT  
 <213> Homo sapien

<400> 575

Met Ala Thr Pro Gly Ser Glu Pro Gln Pro Phe Val Pro Ala Leu Ser  
 1 5 10 15

Val Ala Thr Leu His Pro Leu His His Pro His His His His His His  
 20 25 30

716

His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly  
 35 40 45

Gly Gly Gly Ser Gly Gly Phe Asn Leu Pro Leu Asn Arg Gly Leu Glu  
 50 55 60

Arg Ala Leu Glu Glu Ala Ala Asn Ser Gly Gly Leu Asn Leu Ser Ala  
 65 70 75 80

Arg Lys Leu Lys Glu Phe Pro Arg Thr Ala Ala Pro Gly His Asp Leu  
 85 90 95

Ser Asp Thr Val Gln Ala Asp Leu Ser Lys Asn Arg Leu Val Glu Val  
 100 105 110

Pro Met Glu Leu Cys His Phe Val Ser Leu Glu Ile Leu Asn Leu Tyr  
 115 120 125

His Asn Cys Ile Arg Val Ile Pro Glu Ala Ile Val Asn Leu Gln Met  
 130 135 140

Leu Thr Tyr Leu Asn Leu Ser Arg Asn Gln Leu Ser Ala Leu Pro Ala  
 145 150 155 160

Cys Leu Cys Gly Leu Pro Leu Lys Val Leu Ile Ala Ser Asn Asn Lys  
 165 170 175

Leu Gly Ser Leu Pro Glu Glu Ile Gly Gln Leu Lys Gln Leu Met Glu  
 180 185 190

Leu Asp Val Ser Cys Asn Glu Ile Thr Ala Leu Pro Gln Gln Ile Gly  
 195 200 205

Gln Leu Lys Ser Leu Arg Glu Leu Asn Val Arg Arg Asn Tyr Leu Lys  
 210 215 220

Val Leu Pro Gln Glu Leu Val Asp Leu Pro Leu Val Lys Phe Asp Phe  
 225 230 235 240

Ser Cys Asn Lys Val Leu Val Ile Pro Ile Cys Phe Arg Glu Met Lys  
 245 250 255

Gln Leu Gln Val Leu Leu Leu Glu Asn Asn Pro Leu Gln Ser Pro Pro  
 260 265 270

717

Ala Gln Ile Cys Thr Lys Gly Lys Val His Ile Phe Lys Tyr Leu Ser  
275 280 285

Ile Gln Ala Cys Gln Ile Lys Thr Ala Asp Ser Leu Tyr Leu His Thr  
290 295 300

Met Glu Arg Pro His Leu His Gln His Val Glu Asp Gly Lys Lys Asp  
305 310 315 320

Ser Asp Ser Gly Val Gly Ser Asp Asn Gly Asp Lys Arg Leu Ser Ala  
325 330 335

Thr Glu Pro Ser Asp Glu Asp Thr Val Ser Leu Asn Val Pro Met Ser  
340 345 350

Asn Ile Met Glu Glu Glu Gln Ile Ile Lys Glu Asp Ser Cys His Arg  
355 360 365

Leu Ser Pro Val Lys Gly Glu Phe His Gln Glu Phe Gln Pro Glu Pro  
370 375 380

Ser Leu Leu Gly Asp Ser Thr Asn Ser Gly Glu Glu Arg Asp Gln Phe  
385 390 395 400

Thr Asp Arg Ala Asp Gly Leu His Ser Glu Phe Met Asn Tyr Lys Ala  
405 410 415

Arg Ala Glu Asp Cys Glu Glu Leu Leu Arg Ile Glu Glu Asp Val His  
420 425 430

Trp Gln Thr Glu Gly Ile Ile Ser Ser Ser Lys Asp Gln Asp Met Asp  
435 440 445

Ile Ala Met Ile Glu Gln Leu Arg Glu Ala Val Asp Leu Leu Gln Asp  
450 455 460

Pro Asn Gly Leu Ser Thr Asp Ile Thr Glu Arg Ser Val Leu Asn Leu  
465 470 475 480

Tyr Pro Met Gly Ser Ala Glu Ala Leu Glu Leu Gln Asp Ser Ala Leu  
485 490 495

Asn Gly Gln Ile Gln Leu Glu Thr Ser Pro Val Cys Glu Val Gln Ser  
500 505 510

718

Asp Leu Thr Leu Gln Ser Asn Gly Ser Gln Tyr Ser Pro Asn Glu Ile  
 515 520 525

Arg Glu Asn Ser Pro Ala Val Ser Pro Thr Thr Asn Ser Thr Ala Pro  
 530 535 540

Phe Gly Leu Lys Pro Arg Ser Val Phe Leu Arg Pro Gln Arg Asn Leu  
 545 550 555 560

Glu Ser Ile Asp Pro Gln Phe Thr Ile Arg Arg Lys Met Glu Gln Met  
 565 570 575

Arg Glu Glu Lys Glu Leu Val Glu Gln Leu Arg Glu Ser Ile Glu Met  
 580 585 590

Arg Leu Lys Val Ser Leu His Glu Asp Leu Gly Ala Ala Leu Met Asp  
 595 600 605

Gly Val Val Leu Cys His Leu Val Asn His Ile Arg Pro Arg Ser Val  
 610 615 620

Ala Ser Ile His Val Pro Ser Pro Ala Val Pro Lys Leu Ser Met Ala  
 625 630 635 640

Lys Cys Arg Arg Asn Val Glu Asn Phe Leu Glu Ala Cys Arg Lys Leu  
 645 650 655

Gly Val Pro Glu Ala Asp Leu Cys Ser Pro Cys Asp Ile Leu Gln Leu  
 660 665 670

Asp Phe Arg His Ile Arg Lys Thr Val Asp Thr Leu Leu Ala Leu Gly  
 675 680 685

Glu Lys Ala Pro Pro Pro Thr Ser Ala Leu Arg Ser Arg Asp Leu Ile  
 690 695 700

Gly Phe Cys Leu Val His Ile Leu Phe Ile Val Leu Val Tyr Ile Thr  
 705 710 715 720

Tyr His Trp Asn Ala Leu Ser Ala  
 725

<210> 576

<211> 654

<212> PRT

<213> Homo sapien

719

&lt;400&gt; 576

Met Ala Thr Pro Gly Ser Glu Pro Gln Pro Phe Val Pro Ala Leu Ser  
1 5 10 15

Val Ala Thr Leu His Pro Leu His His Pro His His His His His His  
20 25 30

His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly  
35 40 45

Gly Gly Gly Ser Gly Gly Phe Asn Leu Pro Leu Asn Arg Gly Leu Glu  
50 55 60

Arg Ala Leu Glu Glu Ala Ala Asn Ser Gly Gly Leu Asn Leu Ser Ala  
65 70 75 80

Arg Lys Leu Lys Glu Phe Pro Arg Thr Ala Ala Pro Gly His Asp Leu  
85 90 95

Ser Asp Thr Val Gln Ala Asp Leu Ser Lys Asn Arg Leu Val Glu Val  
100 105 110

Pro Met Glu Leu Cys His Phe Val Ser Leu Glu Ile Leu Asn Leu Tyr  
115 120 125

His Asn Cys Ile Arg Val Ile Pro Glu Ala Ile Val Asn Leu Gln Met  
130 135 140

Leu Thr Tyr Leu Asn Leu Arg Met Ser Ala Ala Thr Glu Ile Thr Ala  
145 150 155 160

Leu Pro Gln Gln Ile Gly Gln Leu Lys Ser Leu Arg Glu Leu Asn Val  
165 170 175

Arg Arg Asn Tyr Leu Lys Val Leu Pro Gln Glu Leu Val Asp Leu Pro  
180 185 190

Leu Val Lys Phe Asp Phe Ser Cys Asn Lys Val Leu Val Ile Pro Ile  
195 200 205

Cys Phe Arg Glu Met Lys Gln Leu Gln Val Leu Leu Leu Glu Asn Asn  
210 215 220

Pro Leu Gln Ser Pro Pro Ala Gln Ile Cys Thr Lys Gly Lys Val His  
225 230 235 240

720

Ile Phe Lys Tyr Leu Ser Ile Gln Ala Cys Gln Ile Lys Thr Ala Asp  
 245 250 255

Ser Leu Tyr Leu His Thr Met Glu Arg Pro His Leu His Gln His Val  
 260 265 270

Glu Asp Gly Lys Lys Asp Ser Asp Ser Gly Val Gly Ser Asp Asn Gly  
 275 280 285

Asp Lys Arg Leu Ser Ala Thr Glu Pro Ser Asp Glu Asp Thr Val Ser  
 290 295 300

Leu Asn Val Pro Met Ser Asn Ile Met Glu Glu Glu Gln Ile Ile Lys  
 305 310 315 320

Glu Asp Ser Cys His Arg Leu Ser Pro Val Lys Gly Glu Phe His Gln  
 325 330 335

Glu Phe Gln Pro Glu Pro Ser Leu Leu Gly Asp Ser Thr Asn Ser Gly  
 340 345 350

Glu Glu Arg Asp Gln Phe Thr Asp Arg Ala Asp Gly Leu His Ser Glu  
 355 360 365

Phe Met Asn Tyr Lys Ala Arg Ala Glu Asp Cys Glu Glu Leu Leu Arg  
 370 375 380

Ile Glu Glu Asp Val His Trp Gln Thr Glu Gly Ile Ile Ser Ser Ser  
 385 390 395 400

Lys Asp Gln Asp Met Asp Ile Ala Met Ile Glu Gln Leu Arg Glu Ala  
 405 410 415

Val Asp Leu Leu Gln Asp Pro Asn Gly Leu Ser Thr Asp Ile Thr Glu  
 420 425 430

Arg Ser Val Leu Asn Leu Tyr Pro Met Gly Ser Ala Glu Ala Leu Glu  
 435 440 445

Leu Gln Asp Ser Ala Leu Asn Gly Gln Ile Gln Leu Glu Thr Ser Pro  
 450 455 460

Val Cys Glu Val Gln Ser Asp Leu Thr Leu Gln Ser Asn Gly Ser Gln  
 465 470 475 480

Tyr Ser Pro Asn Glu Ile Arg Glu Asn Ser Pro Ala Val Ser Pro Thr  
485 490 495

Arg Pro Gln Arg Asn Leu Glu Ser Ile Asp Pro Gln Phe Thr Ile Arg  
515 520 525

Arg Glu Ser Ile Glu Met Arg Leu Lys Val Ser Leu His Glu Asp Leu  
545                      550                      555                      560

Ile Arg Pro Arg Ser Val Ala Ser Ile His Val Pro Ser Pro Ala Val  
580 585 590

Glu Ala Cys Arg Lys Leu Gly Val Pro Glu Glu Lys Leu Cys Leu Pro  
610 615 620

Gln Ala Leu Leu Asp Ile Thr Val Thr Lys Ala Leu Phe Thr  
645 650

<400> 577

Val Ala Thr Leu His Pro Leu His His Pro His His His His His His  
20 25 30

His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly  
35 40 45



722

Gly Gly Gly Ser Gly Gly Phe Asn Leu Pro Leu Asn Arg Gly Leu Glu  
 50 55 60

Arg Ala Leu Glu Glu Ala Ala Asn Ser Gly Gly Leu Asn Leu Ser Ala  
 65 70 75 80

Arg Lys Leu Lys Glu Phe Pro Arg Thr Ala Ala Pro Gly His Asp Leu  
 85 90 95

Ser Asp Thr Val Gln Ala Asp Leu Ser Lys Asn Arg Leu Val Glu Val  
 100 105 110

Pro Met Glu Leu Cys His Phe Val Ser Leu Glu Ile Leu Asn Leu Tyr  
 115 120 125

His Asn Cys Ile Arg Val Ile Pro Glu Ala Ile Val Asn Leu Gln Met  
 130 135 140

Leu Thr Tyr Leu Asn Leu Ser Arg Asn Gln Leu Ser Ala Leu Pro Ala  
 145 150 155 160

Cys Leu Cys Gly Leu Pro Leu Lys Val Leu Ile Ala Ser Asn Asn Lys  
 165 170 175

Leu Gly Ser Leu Pro Glu Glu Ile Gly Gln Leu Lys Gln Leu Met Glu  
 180 185 190

Leu Asp Val Ser Cys Asn Glu Ile Thr Ala Leu Pro Gln Gln Ile Gly  
 195 200 205

Gln Leu Lys Ser Leu Arg Glu Leu Asn Val Arg Arg Asn Tyr Leu Lys  
 210 215 220

Val Leu Pro Gln Glu Leu Val Asp Leu Pro Leu Val Lys Phe Asp Phe  
 225 230 235 240

Ser Cys Asn Lys Val Leu Val Ile Pro Ile Cys Phe Arg Glu Met Lys  
 245 250 255

Gln Leu Gln Val Leu Leu Leu Glu Asn Asn Pro Leu Gln Ser Pro Pro  
 260 265 270

Ala Gln Ile Cys Thr Lys Gly Lys Val His Ile Phe Lys Tyr Leu Ser  
 275 280 285

723.

Ile Gln Ala Cys Gln Ile Lys Thr Ala Asp Ser Leu Tyr Leu His Thr  
 290 295 300

Met Glu Arg Pro His Leu His Gln His Val Glu Asp Gly Lys Lys Asp  
 305 310 315 320

Ser Asp Ser Gly Val Gly Ser Asp Asn Gly Asp Lys Arg Leu Ser Ala  
 325 330 335

Thr Glu Pro Ser Asp Glu Asp Thr Val Ser Leu Asn Val Pro Met Ser  
 340 345 350

Asn Ile Met Glu Glu Glu Gln Ile Ile Lys Glu Asp Ser Cys His Arg  
 355 360 365

Leu Ser Pro Val Lys Gly Glu Phe His Gln Glu Phe Gln Pro Glu Pro  
 370 375 380

Ser Leu Leu Gly Asp Ser Thr Asn Ser Gly Glu Glu Arg Asp Gln Phe  
 385 390 395 400

Thr Asp Arg Ala Asp Gly Leu His Ser Glu Phe Met Asn Tyr Lys Ala  
 405 410 415

Arg Ala Glu Asp Cys Glu Glu Leu Leu Arg Ile Glu Glu Asp Val His  
 420 425 430

Trp Gln Thr Glu Gly Ile Ile Ser Ser Ser Lys Asp Gln Asp Met Asp  
 435 440 445

Ile Ala Met Ile Glu Gln Leu Arg Glu Ala Val Asp Leu Leu Gln Asp  
 450 455 460

Pro Asn Gly Leu Ser Thr Asp Ile Thr Glu Arg Ser Val Leu Asn Leu  
 465 470 475 480

Tyr Pro Met Gly Ser Ala Glu Ala Leu Glu Leu Gln Asp Ser Ala Leu  
 485 490 495

Asn Gly Gln Ile Gln Leu Glu Thr Ser Pro Val Cys Glu Val Gln Ser  
 500 505 510

Asp Leu Thr Leu Gln Ser Asn Gly Ser Gln Tyr Ser Pro Asn Glu Ile  
 515 520 525

724

Arg Glu Asn Ser Pro Ala Val Ser Pro Thr Thr Asn Ser Thr Ala Pro  
 530 535 540

Phe Gly Leu Lys Pro Arg Ser Val Phe Leu Arg Pro Gln Arg Asn Leu  
 545 550 555 560

Glu Ser Ile Asp Pro Gln Phe Thr Ile Arg Arg Lys Met Glu Gln Met  
 565 570 575

Arg Glu Glu Lys Glu Leu Val Glu Gln Leu Arg Glu Ser Ile Glu Met  
 580 585 590

Arg Leu Lys Val Ser Leu His Glu Asp Leu Gly Ala Ala Leu Met Asp  
 595 600 605

Gly Val Val Leu Cys His Leu Val Asn His Ile Arg Pro Arg Ser Val  
 610 615 620

Ala Ser Ile His Val Pro Ser Pro Ala Val Pro Lys Leu Ser Met Ala  
 625 630 635 640

Lys Cys Arg Arg Asn Val Glu Asn Phe Leu Glu Ala Cys Arg Lys Leu  
 645 650 655

Gly Val Pro Glu Glu Lys Leu Cys Leu Pro His His Ile Leu Glu Glu  
 660 665 670

Lys Gly Leu Val Lys Val Gly Ile Thr Ile Gln Ala Leu Leu Asp Ile  
 675 680 685

Thr Val Thr Lys Ala Leu Phe Thr  
 690 695

<210> 578

<211> 58

<212> PRT

<213> Homo sapien

<400> 578

Met Ala Lys Cys Arg Arg Asn Val Glu Asn Phe Leu Glu Ala Cys Arg  
 1 5 10 15

Lys Leu Gly Val Pro Glu Glu Lys Leu Cys Leu Pro His His Ile Leu  
 20 25 30

Glu Glu Lys Gly Leu Val Lys Val Gly Ile Thr Ile Gln Ala Leu Leu  
 35 40 45

725

Asp Ile Thr Val Thr Lys Ala Leu Phe Thr  
 50 55

<210> 579  
 <211> 65  
 <212> PRT  
 <213> Homo sapien

<400> 579

Leu Glu Asp Pro Val Ser Ser Pro Phe Val Cys Val Ile Pro Leu Leu  
 1 5 10 15

Cys Val Ile Arg Ser Ser Ala Lys Ile Arg Ser Thr Glu Glu Lys Leu  
 20 25 30

Cys Leu Pro His His Ile Leu Glu Glu Lys Gly Leu Val Lys Val Gly  
 35 40 45

Ile Thr Ile Gln Ala Leu Leu Asp Ile Thr Val Thr Lys Ala Leu Phe  
 50 55 60

Thr  
 65

<210> 580  
 <211> 536  
 <212> PRT  
 <213> Homo sapien

<400> 580

Met Ala Thr Pro Gly Ser Glu Pro Gln Pro Phe Val Pro Ala Leu Ser  
 1 5 10 15

Val Ala Thr Leu His Pro Leu His His Pro His His His His His  
 20 25 30

His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly  
 35 40 45

Gly Gly Gly Ser Gly Gly Phe Asn Leu Pro Leu Asn Arg Gly Leu Glu  
 50 55 60

Arg Ala Leu Glu Glu Ala Ala Asn Ser Gly Gly Leu Asn Leu Ser Ala  
 65 70 75 80

Arg Lys Leu Lys Glu Phe Pro Arg Thr Ala Ala Pro Gly His Asp Leu

726

85

90

95

Ser Asp Thr Val Gln Ala Asp Leu Ser Lys Asn Arg Leu Val Glu Val  
 100 105 110

Pro Met Glu Leu Cys His Phe Val Ser Leu Glu Ile Leu Asn Leu Tyr  
 115 120 125

His Asn Cys Ile Arg Val Ile Pro Glu Ala Ile Val Asn Leu Gln Met  
 130 135 140

Leu Thr Tyr Leu Asn Leu Ser Arg Asn Gln Leu Ser Ala Leu Pro Ala  
 145 150 155 160

Cys Leu Cys Gly Leu Pro Leu Lys Val Leu Ile Ala Ser Asn Asn Lys  
 165 170 175

Leu Gly Ser Leu Pro Glu Glu Ile Gly Gln Leu Lys Gln Leu Met Glu  
 180 185 190

Leu Asp Val Ser Cys Asn Glu Ile Thr Ala Leu Pro Gln Gln Ile Gly  
 195 200 205

Gln Leu Lys Ser Leu Arg Glu Leu Asn Val Arg Arg Asn Tyr Leu Lys  
 210 215 220

Val Leu Pro Gln Glu Leu Val Asp Leu Pro Leu Val Lys Phe Asp Phe  
 225 230 235 240

Ser Cys Asn Lys Val Leu Val Ile Pro Ile Cys Phe Arg Glu Met Lys  
 245 250 255

Gln Leu Gln Val Leu Leu Leu Glu Asn Asn Pro Leu Gln Ser Pro Pro  
 260 265 270

Ala Gln Ile Cys Thr Lys Gly Lys Val His Ile Phe Lys Tyr Leu Ser  
 275 280 285

Ile Gln Ala Cys Gln Ile Lys Thr Ala Asp Ser Leu Tyr Leu His Thr  
 290 295 300

Met Glu Arg Pro His Leu His Gln His Val Glu Asp Gly Lys Lys Asp  
 305 310 315 320

Ser Asp Ser Gly Val Gly Ser Asp Asn Gly Asp Lys Arg Leu Ser Ala  
 325 330 335

727

Thr Glu Pro Ser Asp Glu Asp Thr Val Ser Leu Asn Val Pro Met Ser  
 340 345 350

Asn Ile Met Glu Glu Glu Gln Ile Ile Lys Glu Asp Ser Cys His Arg  
 355 360 365

Leu Ser Pro Val Lys Gly Glu Phe His Gln Glu Phe Gln Pro Glu Pro  
 370 375 380

Ser Leu Leu Gly Asp Ser Thr Asn Ser Gly Glu Glu Arg Asp Gln Phe  
 385 390 395 400

Thr Asp Arg Ala Asp Gly Leu His Ser Glu Phe Met Asn Tyr Lys Ala  
 405 410 415

Arg Ala Glu Asp Cys Glu Glu Leu Leu Arg Ile Glu Glu Asp Val His  
 420 425 430

Trp Gln Thr Glu Gly Ile Ile Ser Ser Ser Lys Asp Gln Asp Met Asp  
 435 440 445

Ile Ala Met Ile Glu Gln Leu Arg Glu Ala Val Asp Leu Leu Gln Asp  
 450 455 460

Pro Asn Gly Leu Ser Thr Asp Ile Thr Glu Arg Ser Val Leu Asn Leu  
 465 470 475 480

Tyr Pro Met Gly Ser Ala Glu Ala Leu Glu Leu Gln Asp Ser Ala Leu  
 485 490 495

Asn Gly Gln Ile Gln Leu Glu Thr Ser Pro Val Cys Glu Val Gln Ser  
 500 505 510

Asp Leu Thr Leu Gln Ser Asn Gly Ser Gln Tyr Ser Pro Asn Glu Val  
 515 520 525

Ser Phe Leu Lys Ile Asn Gly Arg  
 530 535

<210> 581  
 <211> 317  
 <212> PRT  
 <213> Homo sapien

<400> 581

728

Met Ala Thr Pro Gly Ser Glu Pro Gln Pro Phe Val Pro Ala Leu Ser  
 1 5 10 15  
 Val Ala Thr Leu His Pro Leu His His Pro His His His His His His  
 20 25 30  
 His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly  
 35 40 45  
 Gly Gly Gly Ser Gly Gly Phe Asn Leu Pro Leu Asn Arg Gly Leu Glu  
 50 55 60  
 Arg Ala Leu Glu Glu Ala Ala Asn Ser Gly Gly Leu Asn Leu Ser Ala  
 65 70 75 80  
 Arg Lys Leu Lys Glu Phe Pro Arg Thr Ala Ala Pro Gly His Asp Leu  
 85 90 95  
 Ser Asp Thr Val Gln Ala Asp Leu Ser Lys Asn Arg Leu Val Glu Val  
 100 105 110  
 Pro Met Glu Leu Cys His Phe Val Ser Leu Glu Ile Leu Asn Leu Tyr  
 115 120 125  
 His Asn Cys Ile Arg Val Ile Pro Glu Ala Ile Val Asn Leu Gln Met  
 130 135 140  
 Leu Thr Tyr Leu Asn Leu Ser Arg Asn Gln Leu Ser Ala Leu Pro Ala  
 145 150 155 160  
 Cys Leu Cys Gly Leu Pro Leu Lys Val Leu Ile Ala Ser Asn Asn Lys  
 165 170 175  
 Leu Gly Ser Leu Pro Glu Glu Ile Gly Gln Leu Lys Gln Leu Met Glu  
 180 185 190  
 Leu Asp Val Ser Cys Asn Glu Ile Thr Ala Leu Pro Gln Gln Ile Gly  
 195 200 205  
 Gln Leu Lys Ser Leu Arg Glu Leu Asn Val Arg Arg Asn Tyr Leu Lys  
 210 215 220  
 Val Leu Pro Gln Glu Leu Val Asp Leu Pro Leu Val Lys Phe Asp Phe  
 225 230 235 240  
 Ser Cys Asn Lys Val Leu Val Ile Pro Ile Cys Phe Arg Glu Met Lys

729

245

250

255

Gln Leu Gln Val Leu Leu Leu Glu Asn Asn Pro Leu Gln Ser Pro Pro  
 260 265 270

Ala Gln Ile Cys Thr Lys Gly Lys Val His Ile Phe Lys Tyr Leu Ser  
 275 280 285

Ile Gln Ala Cys Gln Ile Lys Thr Ala Asp Ser Leu Tyr Leu His Thr  
 290 295 300

Met Glu Arg Pro His Leu His Gln His Val Glu Asp Gly  
 305 310 315

<210> 582  
 <211> 179  
 <212> PRT  
 <213> Homo sapien

<400> 582

Met Asn Gly Gly Lys Tyr Ser Pro Leu Glu Ile Arg Glu Asn Ser Pro  
 1 5 10 15

Ala Val Ser Pro Thr Thr Asn Ser Thr Ala Pro Phe Gly Leu Lys Pro  
 20 25 30

Arg Ser Val Phe Leu Arg Pro Gln Arg Asn Leu Glu Ser Ile Asp Pro  
 35 40 45

Gln Phe Thr Ile Arg Arg Lys Met Glu Gln Met Arg Glu Glu Lys Glu  
 50 55 60

Leu Val Glu Gln Leu Arg Glu Ser Ile Glu Met Arg Leu Lys Val Ser  
 65 70 75 80

Leu His Glu Asp Leu Gly Ala Ala Leu Met Asp Gly Val Val Leu Cys  
 85 90 95

His Leu Val Asn His Ile Arg Pro Arg Ser Val Ala Ser Ile His Val  
 100 105 110

Pro Ser Pro Ala Val Pro Lys Leu Ser Met Ala Lys Cys Arg Arg Asn  
 115 120 125

Val Glu Asn Phe Leu Glu Ala Cys Arg Lys Leu Gly Val Pro Glu Glu  
 130 135 140



730

Lys Leu Cys Leu Pro His His Ile Leu Glu Glu Lys Gly Leu Val Lys  
 145 150 155 160

Val Gly Ile Thr Ile Gln Ala Leu Leu Asp Ile Thr Val Thr Lys Ala  
 165 170 175

Leu Phe Thr

<210> 583  
 <211> 77  
 <212> PRT  
 <213> Homo sapien

<400> 583

Met Ala Thr Pro Gly Ser Glu Pro Gln Pro Phe Val Pro Ala Leu Ser  
 1 5 10 15

Val Ala Thr Leu His Pro Leu His His Pro His His His His His His  
 20 25 30

His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly  
 35 40 45

Gly Gly Gly Ser Gly Gly Phe Asn Pro Leu Ser His Pro Leu Pro Val  
 50 55 60

Thr Ser Leu Thr Pro Val Thr Leu Lys Gln Phe Ser Val  
 65 70 75

<210> 584  
 <211> 502  
 <212> PRT  
 <213> Homo sapien

<400> 584

Met Ala Thr Pro Gly Ser Glu Pro Gln Pro Phe Val Pro Ala Leu Ser  
 1 5 10 15

Val Ala Thr Leu His Pro Leu His His Pro His His His His His His  
 20 25 30

His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly  
 35 40 45

Gly Gly Gly Ser Gly Gly Phe Asn Leu Pro Leu Asn Arg Gly Leu Glu  
 50 55 60

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Arg Ala Leu Glu Glu Ala Ala Asn Ser Gly Gly Leu Asn Leu Ser Ala  
 65 70 75 80

Arg Lys Leu Lys Glu Phe Pro Arg Thr Ala Ala Pro Gly His Asp Leu  
 85 90 95

Ser Asp Thr Val Gln Ala Asp Leu Ser Lys Asn Arg Leu Val Glu Val  
 100 105 110

Pro Met Glu Leu Cys His Phe Val Ser Leu Glu Ile Leu Asn Leu Tyr  
 115 120 125

His Asn Cys Ile Arg Val Ile Pro Glu Ala Ile Val Asn Leu Gln Met  
 130 135 140

Leu Thr Tyr Leu Asn Leu Ser Arg Asn Gln Leu Ser Ala Leu Pro Ala  
 145 150 155 160

Cys Leu Cys Gly Leu Pro Leu Lys Val Leu Ile Ala Ser Asn Asn Lys  
 165 170 175

Leu Gly Ser Leu Pro Glu Glu Ile Gly Gln Leu Lys Gln Leu Met Glu  
 180 185 190

Leu Asp Val Ser Cys Asn Glu Ile Thr Ala Leu Pro Gln Gln Ile Gly  
 195 200 205

Gln Leu Lys Ser Leu Arg Glu Leu Asn Val Arg Arg Asn Tyr Leu Lys  
 210 215 220

Val Leu Pro Gln Glu Leu Val Asp Leu Pro Leu Val Lys Phe Asp Phe  
 225 230 235 240

Ser Cys Asn Lys Val Leu Val Ile Pro Ile Cys Phe Arg Glu Met Lys  
 245 250 255

Gln Leu Gln Val Leu Leu Leu Glu Asn Asn Pro Leu Gln Ser Pro Pro  
 260 265 270

Ala Gln Ile Cys Thr Lys Gly Lys Val His Ile Phe Lys Tyr Leu Ser  
 275 280 285

Ile Gln Ala Cys Gln Ile Lys Thr Ala Asp Ser Leu Tyr Leu His Thr  
 290 295 300

732

Met Glu Arg Pro His Leu His Gln His Val Glu Asp Gly Lys Lys Asp  
 305 310 315 320

Ser Asp Ser Gly Val Gly Ser Asp Asn Gly Asp Lys Arg Leu Ser Ala  
 325 330 335

Thr Glu Pro Ser Asp Glu Asp Thr Val Ser Leu Asn Val Pro Met Ser  
 340 345 350

Asn Ile Met Glu Glu Glu Gln Ile Ile Lys Glu Asp Ser Cys His Arg  
 355 360 365

Leu Ser Pro Val Lys Gly Glu Phe His Gln Glu Phe Gln Pro Glu Pro  
 370 375 380

Ser Leu Leu Gly Asp Ser Thr Asn Ser Gly Glu Glu Arg Asp Gln Phe  
 385 390 395 400

Thr Asp Arg Ala Asp Gly Leu His Ser Glu Phe Met Asn Tyr Lys Ala  
 405 410 415

Arg Ala Glu Asp Cys Glu Glu Leu Leu Arg Ile Glu Glu Asp Val His  
 420 425 430

Trp Gln Thr Glu Gly Ile Ile Ser Ser Ser Lys Asp Gln Asp Met Asp  
 435 440 445

Ile Ala Met Ile Glu Gln Leu Arg Glu Ala Val Asp Leu Leu Gln Asp  
 450 455 460

Pro Asn Gly Leu Ser Thr Asp Ile Thr Glu Arg Ser Val Leu Asn Leu  
 465 470 475 480

Tyr Pro Met Gly Ser Ala Glu Ala Leu Glu Leu Gln Asp Ser Ala Leu  
 485 490 495

Lys Tyr Ala Cys Leu Leu  
 500

<210> 585

<211> 151

<212> PRT

<213> Homo sapien

<400> 585

Met Ala Thr Pro Gly Ser Glu Pro Gln Pro Phe Val Pro Ala Leu Ser

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1               5                10                  15

Val Ala Thr Leu His Pro Leu His His Pro His His His His His His
      20                      25                        30

His Gln His His Gly Gly Thr Gly Ala Pro Gly Gly Ala Gly Gly Gly
     35                          40                      45

Gly Gly Gly Ser Gly Gly Phe Asn Leu Pro Leu Asn Arg Gly Leu Glu
   50                            55                        60

Arg Ala Leu Glu Glu Ala Ala Asn Ser Gly Gly Leu Asn Leu Ser Ala
  65                         70                      75                       80

Arg Lys Leu Lys Glu Phe Pro Arg Thr Ala Ala Pro Gly His Asp Leu
        85                                90                             95

Ser Asp Thr Val Gln Ala Asp Leu Ser Lys Asn Arg Leu Val Glu Val
      100                      105                        110

Pro Met Glu Leu Cys His Phe Val Ser Leu Glu Ile Leu Asn Leu Tyr
    115                               120                          125

His Asn Cys Ile Arg Val Ile Pro Glu Ala Ile Val Asn Leu Gln Met
   130                           135                        140

Leu Thr Tyr Leu Asn Leu Arg
0  145                          150

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<210> 586
<211> 51
<212> PRT
<213> Homo sapien
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<400> 586

Met Leu Ala Arg Thr Arg Gly Val Val Val Glu Met Gly Glu Lys Trp  
1 5 10 15

Met Asp Leu Asp Ile Phe Trp Ser Trp Asn Gln Gln Asn Leu Val Met  
20 25 30

Ser Phe Met Cys Ser Leu Arg Lys Gln Glu Met Ile Lys Asp Asp Phe  
35 40 45

Gln Val Leu  
50

734

<210> 587  
 <211> 86  
 <212> PRT  
 <213> Homo sapien

<400> 587

Met Arg Thr Leu Gly Leu Thr Ser Met Glu Asp His Pro Ser Leu Pro  
 1 5 10 15

Arg Ala Arg Asn Pro Met Ala Val Phe His Lys Pro Ala Gly Leu Leu  
 20 25 30

Leu Phe Ser Leu Phe Asn Tyr Thr Ser Leu Gly Val Ala Tyr Met Leu  
 35 40 45

His Leu His Phe Leu Thr Pro Ser Thr Pro Gln Ser Thr Ile Leu Leu  
 50 55 60

Leu Arg Leu Leu Thr Trp Pro Leu Ser Ser Thr Leu Phe Ser Thr Leu  
 65 70 75 80

Thr Cys Pro Gly Ala His  
 85

<210> 588  
 <211> 165  
 <212> PRT  
 <213> Homo sapien

<400> 588

Met Leu Leu Ala Gln Gln Ala Gly Leu Leu Arg Ser Ser Ala Ser Thr  
 1 5 10 15

Leu Leu Val Asp Val Gln Phe Lys Leu His Ser Leu Cys Asp Ser Leu  
 20 25 30

Lys Gly Leu Val Trp Leu Ser Leu Thr Ser Leu Ser Ser Val Pro Gly  
 35 40 45

Asp Thr Leu Phe Pro Ser Ser Arg Leu Val Leu Ser Leu Ala Pro Gly  
 50 55 60

Leu Leu Val Gly Lys Phe Asn Leu Leu Phe Ile Ser Ser Gly Arg Ala  
 65 70 75 80

Thr Val Leu Pro Ser Gly Pro Ser Ser Gly Ile Pro Phe Ala Val Val  
 85 90 95

735

Gly Ala Leu Ile Pro Leu His Val Pro Cys Ser Val Asn Pro Gly Asp  
 100 105 110

Pro Arg Asp Arg Glu Leu Thr Ser Val Phe Phe Ile Trp Cys Ser Met  
 115 120 125

Pro Leu Gly Val Cys Gln Thr Gly Pro Ile Met Trp Val Leu His Leu  
 130 135 140

Phe Thr His Leu Pro Phe Ala Phe Arg Ile Leu Phe Pro Val Gly Asn  
 145 150 155 160

Gly Phe Lys Ser Pro  
 165

<210> 589  
 <211> 104  
 <212> PRT  
 <213> Homo sapien

<400> 589

Met Phe Ser Glu Ala Leu Leu Ile His Arg Thr Tyr Leu Ala Tyr Leu  
 1 5 10 15

Phe Ala Cys Leu Leu Leu Met Ser Ser Leu Thr Glu Ser Leu Leu Gln  
 20 25 30

Arg Thr Thr Pro Ala Ser Arg Pro Arg Asn Val Gly Lys Gly Lys Ala  
 35 40 45

Trp Leu Val Leu Val Glu Met Glu Met Leu Val Thr Val Glu Glu Cys  
 50 55 60

Pro Pro Ser Asp Ser Gln Trp Gly Gly Ala Leu Gly Pro Cys His Cys  
 65 70 75 80

Pro Arg Thr Ser Ala Phe Gly Cys Pro Ala Glu Arg Met Arg His Leu  
 85 90 95

Ser Ser Ser Phe Trp Ser Pro Glu  
 100

<210> 590  
 <211> 165  
 <212> PRT  
 <213> Homo sapien

736

&lt;400&gt; 590

Met Leu Leu Ala Gln Gln Ala Gly Leu Leu Arg Ser Ser Ala Ser Thr  
 1 5 10 15

Leu Leu Val Asp Val Gln Phe Lys Leu His Ser Leu Cys Asp Ser Leu  
 20 25 30

Lys Gly Leu Val Trp Leu Ser Leu Thr Ser Leu Ser Ser Val Pro Gly  
 35 40 45

Asp Thr Leu Phe Pro Ser Ser Arg Leu Val Leu Ser Leu Ala Pro Gly  
 50 55 60

Leu Leu Val Gly Lys Phe Asn Leu Leu Phe Ile Ser Ser Gly Arg Ala  
 65 70 75 80

Thr Val Leu Pro Ser Gly Pro Ser Ser Gly Ile Pro Phe Ala Val Val  
 85 90 95

Gly Ala Leu Ile Pro Leu His Val Pro Cys Ser Val Asn Pro Gly Asp  
 100 105 110

Pro Arg Asp Arg Glu Leu Thr Ser Val Phe Phe Ile Trp Cys Ser Met  
 115 120 125

Pro Leu Gly Val Cys Gln Thr Gly Pro Ile Met Trp Val Leu His Leu  
 130 135 140

Phe Thr His Leu Pro Phe Ala Phe Arg Ile Leu Phe Pro Val Gly Asn  
 145 150 155 160

Gly Phe Lys Ser Pro  
 165

&lt;210&gt; 591

&lt;211&gt; 189

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 591

Met Phe Tyr Met Ser Arg Tyr His Ala Lys Val Leu Leu Gly Ala Ile  
 1 5 10 15

Ala Ser Ala Gly Gln Pro Ala Ser Pro Leu Arg Glu Val Ser Leu Thr  
 20 25 30

737

His Cys Pro Leu Leu Leu Gly Pro Ser Arg Ser His Ile Gln Gly Leu  
 35 40 45

Gly His Tyr Leu Ile Asn Glu Trp Val Val Arg Met Ser Lys Gln Gly  
 50 55 60

Leu Thr Gln Arg Ser Gly Val Thr Gln Pro Gln Lys Leu Arg Val Ser  
 65 70 75 80

Ile Gly Ile Glu Gly Pro Arg Asn Val Phe Phe Val Asp Val Ser Leu  
 85 90 95

Leu Gln Arg Thr Thr Pro Ala Ser Arg Pro Arg Asn Val Gly Lys Gly  
 100 105 110

Lys Ala Trp Leu Val Leu Val Glu Met Glu Met Leu Val Thr Val Glu  
 115 120 125

Glu Cys Pro Pro Ser Asp Ser Gln Trp Gly Gly Ala Leu Gly Pro Cys  
 130 135 140

His Cys Pro Arg Thr Ser Gly Lys Ser Ala Arg Gly Pro Gln Pro Phe  
 145 150 155 160

Pro Ala Arg Arg Pro Gly Arg Arg Leu Val Leu Thr Ser Met Arg Phe  
 165 170 175

Leu Asp Gly Thr Ala Ser Leu Leu Ser Lys Pro Phe Leu  
 180 185

<210> 592

<211> 86

<212> PRT

<213> Homo sapien

<400> 592

Met Arg Thr Leu Gly Leu Thr Ser Met Glu Asp His Pro Ser Leu Pro  
 1 5 10 15

Arg Ala Arg Asn Pro Met Ala Val Phe His Lys Pro Ala Gly Leu Leu  
 20 25 30

Leu Phe Ser Leu Phe Asn Tyr Thr Ser Leu Gly Val Ala Tyr Met Leu  
 35 40 45

His Leu His Phe Leu Thr Pro Ser Thr Pro Gln Ser Thr Ile Leu Leu



738

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55

60

Leu Arg Leu Leu Thr Trp Pro Leu Ser Ser Thr Leu Phe Ser Thr Leu  
 65 70 75 80

Thr Cys Pro Gly Ala His  
 85

<210> 593  
 <211> 24  
 <212> PRT  
 <213> Homo sapien

<400> 593

Met Tyr Leu Thr Ser Phe Leu Val Phe Ser Ser Glu Ser Arg Asp Asp  
 1 5 10 15

Asp Asp Asn Val Thr Ser His Asp  
 20

<210> 594  
 <211> 30  
 <212> PRT  
 <213> Homo sapien

<400> 594

Met Val Ile Tyr Gln Ser Pro Leu Gln Phe Leu Thr Trp Ser Ser Thr  
 1 5 10 15

Ser Arg Lys Ser Ser Phe Leu Ser Gln Arg Val Leu Gly Pro  
 20 25 30

<210> 595  
 <211> 94  
 <212> PRT  
 <213> Homo sapien

<400> 595

Met Gly Lys Asp Leu Thr Pro Ile Thr Pro Ser Ser Gly Phe Thr Ile  
 1 5 10 15

Glu Leu Ala Ser Ala Phe Thr Val Val Ile Ala Ser Asn Ile Gly Leu  
 20 25 30

Pro Val Ser Thr Thr His Cys Lys Val Gly Ser Val Val Ala Val Gly  
 35 40 45

Trp Ile Arg Ser Arg Lys Ala Val Asp Trp Arg Leu Phe Arg Asn Ile

739

50

55

60

Phe Val Ala Trp Phe Val Thr Val Pro Val Ala Gly Leu Phe Ser Ala  
 65 70 75 80

Ala Val Met Ala Leu Leu Met Tyr Gly Ile Leu Pro Tyr Val  
 85 90

<210> 596  
 <211> 94  
 <212> PRT  
 <213> Homo sapien

<400> 596

Met Gly Lys Asp Leu Thr Pro Ile Thr Pro Ser Ser Gly Phe Thr Ile  
 1 5 10 15

Glu Leu Ala Ser Ala Phe Thr Val Val Ile Ala Ser Asn Ile Gly Leu  
 20 25 30

Pro Val Ser Thr Thr His Cys Lys Val Gly Ser Val Val Ala Val Gly  
 35 40 45

Trp Ile Arg Ser Arg Lys Ala Val Asp Trp Arg Leu Phe Arg Asn Ile  
 50 55 60

Phe Val Ala Trp Phe Val Thr Val Pro Val Ala Gly Leu Phe Ser Ala  
 65 70 75 80

Ala Val Met Ala Leu Leu Met Tyr Gly Ile Leu Pro Tyr Val  
 85 90

<210> 597  
 <211> 82  
 <212> PRT  
 <213> Homo sapien

<400> 597

Ala Ser Ser Ser Pro Ala Pro Pro Gly Lys His Gly Glu Gly Arg Gln  
 1 5 10 15

Glu Glu Val Gln Val Cys Pro Pro Pro Ile His Cys Pro Lys Thr Arg  
 20 25 30

Trp Glu Arg Lys Glu Leu Phe Leu Glu Val Glu Leu His Val Arg Asn  
 35 40 45

740

Cys Asn Gly Leu Trp Trp Ala Arg Trp Trp Pro Trp Ala Gly Ser Ala  
 50 55 60

Pro Ala Arg Leu Trp Thr Gly Ala Ser Phe Gly Thr Ser Ser Trp Pro  
 65 70 75 80

Gly Ser

<210> 598  
 <211> 144  
 <212> PRT  
 <213> Homo sapien

<400> 598

Ala Gly Glu Thr Gln Arg Arg Pro Gln Cys Arg Pro Arg Ala Arg Glu  
 1 5 10 15

Trp Ser Arg Ala Pro Phe Pro Tyr Arg Ala Ala Thr Pro Ala Arg Ala  
 20 25 30

Ala Arg Ala Ala Ser Arg Glu Pro Pro Ala Arg Leu Pro Gly Ser Arg  
 35 40 45

Gly Trp Gly Pro Gly Leu Val Gly Ala Gly Gly Ala Arg Gly Gly Gly  
 50 55 60

Gly Leu Arg Pro Pro Arg Leu Leu Ala His Val Asp Leu Ala Val Ala  
 65 70 75 80

Cys Arg Ala Ala Pro Leu Arg Lys Leu Asp Gly Ser Gly Arg Asp Arg  
 85 90 95

Ala Leu Pro Ala Ser Ala Gly Arg Leu Leu Leu Arg Cys Ala Arg Leu  
 100 105 110

Gly Trp Asp Ser Ala Gly Glu Gly Ser Cys Thr Leu Ser His Gln Ala  
 115 120 125

Gln Cys Ser Arg Ala Ala Gln Arg Ile Ser Phe Leu Val Leu Arg Ala  
 130 135 140

<210> 599  
 <211> 151  
 <212> PRT  
 <213> Homo sapien

<400> 599

741

Met Leu Gly Arg Gly Gln Asn Leu Pro Arg Asp Pro Glu Gly Gln Asn  
 1 5 10 15

Thr Leu Glu Gly Pro Gly Ile Leu Met Ser Pro Leu Ser Pro Arg Trp  
 20 25 30

Phe Ser Gly Met Glu Lys Ala Pro Cys Pro Pro Leu Glu Pro Cys Ser  
 35 40 45

Arg Ala Asp Glu Thr Pro Ala Arg Pro Ala Glu His Tyr Ser Arg Met  
 50 55 60

Lys Glu Ser Gln Arg Lys Arg Gln Met Cys Trp Pro Val Asn Ser Leu  
 65 70 75 80

Ile Ser Asn Val Asn Gln Ile Gln Ala His Asp Ile Arg Ser Ala Ser  
 85 90 95

Pro Thr Val Gly Ile Leu Cys Gly Pro Ile Val Trp Thr Val Trp Val  
 100 105 110

Arg Ser Leu Trp Leu Phe Cys Asp Ala Cys Val Gly Ser Ser Leu Ser  
 115 120 125

Ala Gln Lys Leu Gln Thr Leu Trp Asn Arg Phe Ser Gly Pro Val Ala  
 130 135 140

Val Thr Pro Ala Leu Glu Thr  
 145 150

<210> 600

<211> 127

<212> PRT

<213> Homo sapien

<400> 600

Met Ser Pro Leu Ser Pro Arg Trp Phe Ser Gly Met Glu Lys Ala Pro  
 1 5 10 15

Cys Pro Pro Leu Glu Pro Cys Ser Arg Ala Asp Glu Thr Pro Ala Arg  
 20 25 30

Pro Ala Glu His Tyr Ser Arg Met Lys Glu Ser Gln Arg Lys Arg Gln  
 35 40 45

Met Cys Trp Pro Val Asn Ser Leu Ile Ser Asn Val Asn Gln Ile Gln

742

50

55

60

Ala His Asp Ile Arg Ser Ala Ser Pro Thr Val Gly Ile Leu Cys Gly  
 65 70 75 80

Pro Ile Val Trp Thr Val Trp Val Arg Ser Leu Trp Leu Phe Cys Asp  
 85 90 95

Ala Cys Val Gly Ser Ser Leu Ser Ala Gln Lys Leu Gln Thr Leu Trp  
 100 105 110

Asn Arg Phe Ser Gly Pro Val Ala Val Thr Pro Ala Leu Glu Thr  
 115 120 125

&lt;210&gt; 601

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 601

Met Cys His Ile Ala Lys Gly Lys Ser Leu Ile Ser Arg Pro Asn Phe  
 1 5 10 15

Asn Gln Ile Val Asn Leu Thr His Tyr Ile Phe Val Asn Met  
 20 25 30

&lt;210&gt; 602

&lt;211&gt; 191

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 602

Met Arg Glu Ser Ser Ser Gly Phe Pro Ser Pro Ala Glu Val Pro Val  
 1 5 10 15

Leu Ala Thr Ser Leu Pro Ile His Arg Trp Gly Arg Pro Ala Ala His  
 20 25 30

Pro Pro Cys His Cys Gln Val Pro Trp Ala Ser Ser Pro His Leu Leu  
 35 40 45

Ser Pro Gln Ser Ala Cys Cys Arg Trp Thr Val Lys Ile His Trp Trp  
 50 55 60

Thr Val His Leu Ser Leu Val Thr Leu Arg Cys Ser Leu Arg Ile Phe  
 65 70 75 80

743

Val Pro Leu Pro Gln Glu Val Val Val Ser Gln Pro Ser Cys Gln Asp  
85 90 95

Leu Thr Leu Ile Val Val Tyr Gln Glu Thr Cys Arg Leu Pro Ser Tyr  
100 105 110

Ser Arg His Val Gly Met Tyr Leu Thr Val Leu Leu Gln Asn Ile Asp  
115 120 125

Arg His Ile Thr Asp Gly Pro Cys Leu Met Glu Ile Arg Pro Gln Leu  
130 135 140

Val	Gln	Leu	Leu	Ser	Gln	Pro	Leu	Glu	Pro	Leu	His	Cys	His	Ser	Ala
145					150					155					160

Pro His Leu Leu Leu Thr Val Ile Cys Gln Gly Arg Ser His Pro Arg  
165 170 175

Ser Thr Ala Leu Ser Thr Ser Cys Leu Ser Val Ala Leu Pro Pro  
180 185 190

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<210> 603
<211> 134
<212> PRT
<213> Homo sapien
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<400> 603

Met Glu Leu Arg Ser Arg Glu Glu Glu Leu Thr Arg Ala Ala Leu Gln  
1 5 10 15

Gln Lys Ser Gln Glu Glu Leu Leu Lys Arg Arg Glu Gln Gln Leu Ala  
20 25 30

Glu Arg Glu Ile Asp Val Leu Glu Arg Glu Leu Asn Ile Leu Ile Phe  
35 40 45

Gln Leu Asn Gln Glu Lys Pro Lys Val Lys Lys Arg Lys Gly Lys Phe  
50 55 60

Lys Arg Ser Arg Leu Lys Leu Lys Asp Gly His Arg Ile Ser Leu Pro  
65 70 75 80

Ser Asp Phe Gln His Lys Ile Thr Val Gln Ala Ser Pro Asn Leu Asp  
85 90 95

Lys Arg Arg Ser Leu Asn Ser Ser Ser Ser Ser Pro Pro Ser Ser Pro  
100 105 110

744

Thr Met Met Pro Arg Leu Arg Ala Ile Gln Cys Glu Leu Ser Ala Leu  
 115 120 125

Pro Arg Gly Leu Leu Cys  
 130

<210> 604  
 <211> 43  
 <212> PRT  
 <213> Homo sapien

<400> 604

Met His Gln Gly Phe Phe Ser Leu Tyr Leu Glu Tyr Ser Leu Ser Ser  
 1 5 10 15

Ser Ser Ser Gly Trp Leu Leu Pro Ser Phe Arg Ser Trp Val Arg Cys  
 20 25 30

Cys Phe Ser Gly Thr Leu Cys Tyr Asn His Phe  
 35 40

<210> 605  
 <211> 55  
 <212> PRT  
 <213> Homo sapien

<400> 605

Met Lys Lys Glu Gln Met Ile Leu Arg Arg Val Pro Asp Ile Arg Lys  
 1 5 10 15

Leu Thr Pro Lys Gly Thr Ser Lys Ala Asn Trp Leu Gln Arg Pro Thr  
 20 25 30

Thr Arg Lys Glu Ser Ser Gly Val Gly Leu Cys Thr Gly Asp Asn Gly  
 35 40 45

Arg Ile Cys Gly Cys Ser Ser  
 50 55

<210> 606  
 <211> 55  
 <212> PRT  
 <213> Homo sapien

<400> 606

Met Leu Val Ser Ser Cys Ala Phe Ile Asn Leu Ala Lys Pro Glu Cys  
 1 5 10 15

745

Ser Thr Phe Arg Ser Glu Val Pro Val Leu Ile Ala His Pro Tyr Ser  
                   20                                  25                                  30

Ile Ser Glu Ser Gly Ile Glu Thr Phe Ala Ile Tyr Tyr Phe Pro Phe  
           35                                  40                                  45

His Gln His Pro Pro Thr Cys  
           50                                  55

<210> 607  
 <211> 35  
 <212> PRT  
 <213> Homo sapien

<400> 607

Met Leu Ile Asp Leu Leu His Cys His Ser Gln Lys Gln Trp Gln Tyr  
   1                                  5                                  10                                  15

Phe Val Ser Ile Val Met Lys Leu Phe Ala Leu Ile Gly Phe Tyr Ser  
                   20                                  25                                  30

Gly Ser Ala  
           35

<210> 608  
 <211> 85  
 <212> PRT  
 <213> Homo sapien

<400> 608

Met Glu Glu Ala Ser Thr Cys Pro Ser Gly Ser Gln Ser Pro Cys Leu  
   1                                  5                                  10                                  15

Ser Val Leu Pro Asp Gln Phe Leu Cys Met Ala Leu His Pro Ser Pro  
                   20                                  25                                  30

Arg Ala Phe Leu Leu Pro Ser Asp Gln Arg Ile Asp Val Glu Leu Trp  
           35                                  40                                  45

Ala Glu Gln Ala Glu Leu Asn Ser Thr Glu Leu His Gln Met Arg Val  
           50                                  55                                  60

Gln Asp Asn Cys Leu Phe Ser Ile Ser Pro Lys Ala Gly Ser Leu Ser  
   65                                  70                                  75                                  80

Pro Leu Gly Ser Ser



746

85

<210> 609  
 <211> 65  
 <212> PRT  
 <213> Homo sapien

<400> 609

Met Gly Arg Gly Ala Leu Ser Ser Cys Cys Thr Arg Gln Ala Pro Ser  
 1 5 10 15

Pro Ser Cys Ser Lys Leu Glu Pro Ala Ser Cys Arg Pro Cys Gln His  
 20 25 30

Pro Gly Trp Gly Arg Asp Gln Val Val Gly Glu Val Glu Lys Gly Leu  
 35 40 45

Ser Gly Trp Ser Ala Ala Ala Glu Lys Gln Gln Lys Arg Asn Gly Glu  
 50 55 60

Gly  
 65

<210> 610  
 <211> 138  
 <212> PRT  
 <213> Homo sapien

<400> 610

Ser Leu Glu Gly Arg Val Val Arg Arg Arg Gln Pro Pro Ser Gly Arg  
 1 5 10 15

Gly Ser Phe Leu Val Thr Glu Asn Tyr Cys Pro Phe Thr Pro Gly Pro  
 20 25 30

Asn Phe Pro Ser Pro Pro Pro Thr Ile His Pro Lys Thr Ala Val Ala  
 35 40 45

Gly His Tyr Gln Gly Ser Gly Leu Ser Ser Arg Ser Leu Leu Arg Cys  
 50 55 60

Ser Ala Ala Thr Gly Arg Gly Leu Pro Val Pro Gly Arg Pro Ala Gly  
 65 70 75 80

Ala Gly Leu His Gly Glu Gly Gly Thr Gln Gln Leu Leu Tyr Glu Ala  
 85 90 95

747

Gly Pro Leu Pro Leu Leu Leu Lys Ala Gly Ala Cys Phe Leu Ser Ser  
100 105 110

Leu Ser Ala Pro Trp Val Gly Glu Gly Pro Gly Ser Gly Gly Ser Gly  
115 120 125

Lys Gly Ile Glu Arg Leu Glu Cys Ser Ser  
130 135

&lt;210&gt; 611

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 611

Met Glu Lys Val Ser Pro Ile Trp Arg Gln Ser Ser Val Phe Pro Ile  
1 5 10 15

Gly Asn Arg Gln Asn Lys Arg  
20

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(71) Applicant (*for all designated States except US*): DI-ADEXUS, INC. [US/US]; 343 Oyster Point Boulevard, South San Francisco, CA 94080 (US).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): SUN, Yongming [CN/US]; 551 Shoal Drive, Redwood City, CA 94065 (US). LIU, Chenghua [CN/US]; 1125 Ranchero Way #14, San Jose, CA 95117 (US).

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(74) Agents: LICATA, Jane, Massey et al.; Licata & Tyrrell P.C., 66 E. Main Street, Marlton, NJ 08053 (US).

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMPOSITIONS AND METHODS RELATING TO HEPATIC SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acid molecules and polypeptides present in normal and neoplastic hepatic cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions containing the nucleic acid molecules, polypeptides, antibodies, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating hepatic cancer and non-cancerous disease states in hepatic, identifying hepatic tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered hepatic tissue for treatment and research.



WO 2003/066877 A3

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/41349

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C12N 1/21, 15/12, 15/63; C07K 14/435; C12Q 1/68

US CL : 435/6, 69.1, 320.1, 252.3; 536/23.5; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 69.1, 320.1, 252.3; 536/23.5; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database GenBank, Accession Number AL139328.8, WALL, M., Direct Submission. 04 April 2001.	1-12

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier application or patent published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*A\*

document member of the same patent family

Date of the actual completion of the international search

05 September 2003 (05.09.2003)

Date of mailing of the international search report

11 DEC 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

John S. Brusca

Telephone No. 703 308-0196

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/41349

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-12 and SEQ ID NOS: 1 and 410

Remark on Protest

☐  
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-12, drawn to polynucleotides, polypeptides, their method of making and using (1<sup>st</sup> product, 1<sup>st</sup> method of making, 1<sup>st</sup> method of using).

Group II, claim(s) 13, drawn to antibodies (2<sup>nd</sup> product).

Group III, claim(s) 14, drawn to a hepatic specific protein assay (2<sup>nd</sup> method of use).

Group IV, claim(s) 15, drawn to a hepatic cancer diagnostic assay (3<sup>rd</sup> method of use).

Group V, claim(s) 16, drawn to an assay kit (3<sup>rd</sup> product).

Group VI, claim(s) 17, drawn to a hepatic cancer therapeutic method (4<sup>th</sup> method of use).

Group VII, claim(s) 18, drawn to a vaccine (4<sup>th</sup> product).

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

In Group IV, a polynucleotide diagnostic species and a polypeptide diagnostic species  
In Group V, a polynucleotide assay kit species and a polypeptide assay kit species  
In Group VI, a polynucleotide therapeutic species and a polypeptide therapeutic species  
In Group VII, a polynucleotide vaccine species and a polypeptide vaccine species

The claims are deemed to correspond to the species listed above in the following manner:

Claim 15 corresponds to the species of Group IV  
Claim 16 corresponds to the species of Group V  
Claim 17 corresponds to the species of Group VI  
Claim 18 corresponds to the species of Group VII

The following claim(s) are generic: Claims 15-18 are Markush-type claims.

In addition, each Group detailed above reads on distinct Groups drawn to multiple sequences. The sequences are distinct because they are unrelated sequences, and a further lack of unity is applied to each Group. The Applicants must further elect one corresponding set of polynucleotide and polypeptide sequences for examination in the elected Group detailed above. Payment of fees for an additional invention will entitle the Applicants to examination of one additional set of sequences.

The total number of inventions was calculated based on the number of combinations that exist between the SEQ ID numbers and the total number of groups. The formula is recited below:

Total Number of Inventions = ((number of Groups + (Number of species - number of Groups)) X Total SEQ ID NOS)

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Each sequence set of polynucleotide and polypeptide lack a common special technical feature because each sequence corresponds to a different polypeptide with a different biological property. In addition PCT Rule 13.1 and Annex B do not provide for unity of invention between two or more different products, methods of making, or methods of using that share a special technical feature.

# INTERNATIONAL SEARCH REPORT

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The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The species use or comprise compositions with different structures that produce different biological effects.

## Continuation of B. FIELDS SEARCHED Item 3:

GenEMBL, GenSeq, Issued and Published US Patent sequence databases, EST databases  
search terms: SEQ ID NOS: 1 and 410

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